EVALUATION OF ADVANCED CLINICOPATHOLOGICAL AND STRUCTURAL ASPECTS OF MODERN ONCOPLASTIC BREAST CANCER SURGERY

Ph.D. Thesis

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LIST OF FULL PAPERS THAT SERVED AS THE BASIS OF THE PH.D. THESIS

I. Dorogi B, Bukovszky B, Mátrai T, Sávolt Á, Polgár Cs, Kelemen P, Kovács T, Rényi-Vámos F, Ivády G, Kovács E, Téglás T, Kásler M, Mátrai Z.

Mapping of the functional anatomy of lymphatic drainage to the axilla in early breast cancer: A cohort study of 933 cases.
Eur J Surg Oncol. 2019 Feb; 45(2):103-109. doi: 10.1016/j.ejso.2018.08.030. Epub 2018 Oct 7.
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II. Dorogi B, Pukancsik D, Újhelyi M, Mátrai T, Kenessey I, Sávolt Á, Ping O, Huszár O, Mészáros N, Ivády G, Kovács E, Mátrai Z.

Clinicopathological correlations of areola-sparing mastectomy versus nipple-sparing mastectomy: a single-centre retrospective study of 227 cases.
Breast J. 2020 Jul 1. doi: 10.1111/tbj.13957. Online ahead of print.
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III. Dorogi B, Mátrai T, Újhelyi M, Kenessey I, Kelemen P, Sávolt Á, Huszár O, Ping O, Pukancsik D, Mátrai Z.

Assessing the needs of Hungarian breast cancer patients for modern oncoplastic breast surgical treatment – questionnaire study of 500 patients.
Orv Hetil. 2020 Jul;161(29):1221-1228. doi: 10.1556/650.2020.31768.
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OTHER PUBLICATIONS RELATED TO THE THEME OF THE THESIS

I. Dorogi B, Gulyás G, Kunos Cs, Udvarhelyi N, Mátrai Z.

Contralateral axillary silicone lymphadenopathy after modified radical mastectomy and reconstruction.

Eur J Plast Surg. 2014 Jun; 37:505–508. doi: 10.1007/s00238-014-0970-4.
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II. Mátrai Z, Tóth L, Saeki T, Sinkovics I, Godény M, Takeuchi H, Bidlek M, Bartal A, Sávolt A, **Dorogi B**, Kásler M.

The potential role of SPECT/CT in the preoperative detection of sentinel lymph nodes in breast cancer.
Orv Hetil. 2011 Apr;152(17):678-88. doi: 10.1556/OH.2011.29077.
IF: 0.000

III. Dorogi B, Pálházi P.

Az emlő és a regionális nyirokelvezetés anatómiája
In: Mátrai Z, Gulyás G, Kásler M: Az emlőrák korszerű sebészete
Medicina, Budapest, 2015; 39-47.
IF: 0.000

∑ 0.000

CONTENTS

LIST OF ABBREVIATIONS

ACOSOG - American College of Surgeons Oncology Group
ALND – axillary lymph node dissection
AMAROS – After Mapping of the Axilla: Radiotherapy Or Surgery
ARM - axillary reverse mapping
ASM - areola-sparing mastectomy
BCS – breast-conserving surgery
BRESO - An European international educational and accreditation project
BU – breast unit
CEEBCSC - Central-Eastern European Breast Cancer Surgical Consortium
DFS – disease-free survival
EBCC - European Breast Cancer Conference
EUBRAST - European Breast Cancer Research Association of Surgical Trialists
ECIBC - European Commission Initiative on Breast Cancer
EORTC - European Organization for Research and Treatment of Cancer
ESMO - European Society of Medical Oncology
ESO - European School of Oncology
ESSO - European Society of Surgical Oncology
ESTRO - European Society for Radiotherapy and Oncology
EBSQ - European Board of Surgery Qualification
EUSOMA - European Society of Mastology
G.Re.T.A. - Group for Reconstructive and Therapeutic Advancements
HTgF - high tangential field
NAC - nipple-areola complex
NACT - neoadjuvant chemotherapy
NEAK - National Health Insurance Fund of Hungary, Nemzeti Egészségbiztosítási Alapkezelő
NIO - National Institute of Oncology, Országos Onkológiai Intézet
NSM - nipple-sparing mastectomy
OS - overall survival
OTOASOR - Optimal Treatment Of the Axilla – Surgery or Radiotherapy
PMRT - postmastectomy radiotherapy
PROM - patient-reported outcome measure
QoL - quality of life
RT - radiotherapy
RTOG - Radiation Therapy Oncology Group
SD - standard deviation
SLN - sentinel lymph node
SLNB - sentinel lymph node biopsy
SSM - skin-sparing mastectomy
STgF - standard tangential field
TDLU - terminal ductal lobular unit
UEMS - European Union of Medical Specialists
WBI - whole breast irradiation

TABLE OF CONTENTS

LIST OF FIGURES

1. Introduction

Breast cancer is the most common malignancy in women with more, than 8.400 newly diagnosed cases and nearly 2.200 deaths in 2017, according to the Hungarian National Cancer Registry [1]. Breast cancer treatment has gone through a long evolutional process from Halsted's procedure to nowadays' complex multidisciplinary approach and oncoplastic surgical procedures on the last decades [2-4]. The introduction of populational based breast screening programmes, supported by the development of molecular biology, histology, radio-, and oncotherapy resulted in a significant increase in five-year survival rate (from 52% to 85.1%) [5-7].

With the scientific endorsement of oncoplastic breast surgery, the main focus of breast cancer treatment shifted to higher level issues targeting treatment optimization by the de-escalation or escalation of the current protocols [8]: active surveillance or surgery for low-risk DCIS, the role and indication of nipple-sparing mastectomy (NSM), questions of the surgical margins, sentinel lymph node biopsy (SLNB) after neoadjuvant chemotherapy (NACT), omitting axillary lymph node dissection (ALND) or targeted axillary surgery [9-13].

The hypotheses of this dissertation also aimed to evaluate advanced level issues of modern breast surgery: the correlations of the lymphatic drainage pattern of the breast which may provide further basic information for the interpretation of American College of Surgeons Oncology Group (ACOSOG) Z0011, Optimal Treatment Of the Axilla – Surgery or Radiotherapy (OTOASOR) and After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) trials; the cosmetic role and oncologic importance of the nipple-areola complex (NAC) and its components in the context of the preservation of the complex anatomical unit of the nipple by NSMs or only the pigmented kin of the areola by areola-sparing mastectomies (ASM) and today's yet invisible questions, the needs and requirements of the Hungarian health care system due to the rapid expansion of oncoplastic breast surgery.

1.1. Anatomy of the subregions of the axilla and its importance in breast cancer treatment

Anatomically, the axillary region is divided into five subregions: anterior, posterior, lateral, central and apical zones [14] (Figure 1.).

The anterior subregion is located under the lateral edge of the pectoralis minor muscle along the lateral thoracic vein. The posterior zone is found adjacent to the posterior wall of the axilla along the thoracodorsal nerve and vessels. The lateral subregion is located close to the lateral wall of the axilla, in relation to the proximal part of the axillary vein. The lymph nodes in this zone receive the vast majority of the efferent lymph vessels of the upper limb. The central zone is in the middle of the pyramid-shaped space of the armpit, close to the base of the axilla. The apical subregion is found in the apex medially to the distal part of the axillary vein.

These subregions correspond to the axillary node levels previously described by Berg [15]. The anterior, posterior and lateral subregions constitute Level I, the central zone forms Level II and the apical zone constitutes Level III [14].

Clear relationships between the anatomic location and metastatic status of the sentinel lymph node (SLN) have been revealed [16, 17]. Histologically positive SLN was detected in Level I in 96% of cases and in Level II in 4% of cases by SPECT/CT [17].

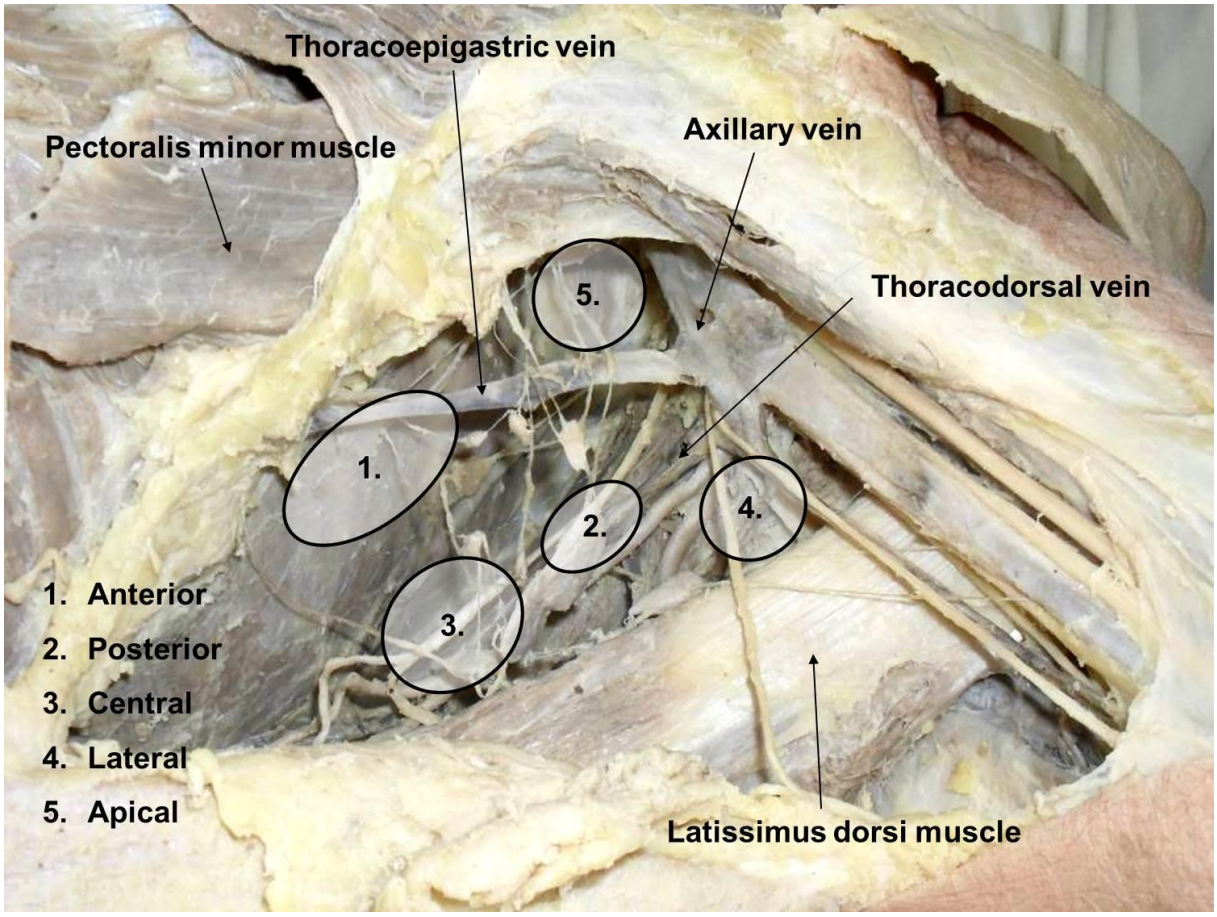

Figure 1. *Subregions of the axilla (left side, human cadaveric dissection)*

Regional lymph node status is one of the most important prognostic factors for disease-free (DFS) and overall survival (OS) in breast cancer [18-22]. Today, the gold-standard method for staging patients with early-stage breast cancer with clinically negative axillary lymph nodes is the SLNB [21, 22].

To optimise the effectiveness of SLNB, the precise pre- and intraoperative mapping of lymphatic drainage is mandatory[21-23].

A better understanding of the relationships between the subregional drainage pattern of SLN, the subregional localisation of SLN and the correlation to location and pathological characteristics of the primary breast tumour could have particular importance in determining whether ALND can be safely omitted.

The ACOSOG Z0011 trial did not perform ALND for early-stage breast cancer patients with 1-2 metastatic SLNs (cT1-2, pN1), and in the majority of the patients, the axilla was treated only with tangential field irradiation following breast-conserving surgery (BCS). After a median follow-up of 9.3 years, the data compared to the traditional ALND group showed no differences in local recurrence-free survival [24, 25]. However, in the ACOSOG Z0011 trial, dose distribution in the axillary volumes was not reported in the initial publication. Jagsi et al. [26] recently analysed the radiotherapy (RT) coverage of the axillary lymph nodes of that trial. Most patients treated in the Z0011 trial received tangential RT alone, and some received no RT at all. Some patients received directed nodal irradiation via a third field. They concluded that further research is necessary to determine the optimal RT approach in patients with low-volume axillary disease treated with SLNB alone.

A recent surgical technique that is less radical and therefore decreases the morbidity of SLNB and ALND, especially lymphedema, is axillary reverse mapping (ARM) [27-29]. The lymphatic drainage of the upper limb that runs through the axilla - most often the lateral subregional lymphatic structures - is identified by injecting radioisotope or blue dye to the ipsilateral limb subcutaneously, and these nodes are spared during the operation, removing only the lymph nodes that drain the lymph of the breast. The technique was proven to be feasible with a low level of evidence; however, the question of oncological radicality still arises due to the uncertainty of the metastatic status of the ARM lymph nodes that are not removed [30].

1.2. Anatomy of the nipple-areola complex and its importance in breast cancer treatment

In recent decades, several types of mastectomy have been developed to enhance the cosmetic outcomes of immediate breast reconstructions and therefore patient satisfaction; these techniques include skin-sparing mastectomy (SSM), ASM and NSM. As a consequence, concerns of oncological safety have arisen in regard to not compromising cancer treatment by preserving the skin, especially the nipple [31, 32].

The main question behind the possible uncertainty of NSM is the anatomy of the NAC and the chance of cancer development in the remnant tissue after mastectomy. The nipple contains the ducts draining the mammary gland, but terminal ductal lobular units (TDLUs) - from where ductal and lobular breast cancer arise – can also be found in the NAC [33-37]. A recent anatomical study by Rusby et al. showed that the ducts form a central bundle in the nipple that narrows just under the skin before spreading to the breast parenchyma [38]. The central bundle is covered by a duct-free rim of tissue containing 50% of the vasculature of the nipple, allowing a complete ductal resection leaving a 2-mm peripheral rim behind without damaging the blood supply in 96% of the cases [39]. TDLUs can be present behind the areola in up to 25-26% of cases [34, 36], but are located at the base of the nipple [37]. By understanding these sophisticated anatomical details, the duct core and the possible TDLUs can be excised by applying a careful dissection at the level of the dermis below the NAC, resulting in an oncologically safe and cosmetically superior nipple-sparing procedure [36, 40-42].

Up until the dispelling of oncological concerns regarding the preservation of the nipple, SSM was the preferred procedure for delayed-immediate breast reconstruction for suitable patients. Since the acceptance of NSM at the 13th St. Gallen International Breast Cancer Conference [43] and strengthening of its role and the broadening of its indications in the surgical treatment of breast cancer at the Oncoplastic Breast Consortium consensus conference on NSM in Basel [13], the importance of ASM has largely been reduced.

However, if the nipple has to be removed for oncological reasons, the complexity of the anatomical and aesthetical substructure of the NAC comes into the highlight. In such indications the oncological and cosmetic importance (as well patient reported outcomes) of the nipple and separately the pigmented skin of the areola should have better known by the modern breast oncoplastic surgery.

1.3. The Hungarian system of oncoplastic breast cancer care and its requirements

Due to inequalities in special needs oncology care, the first European Breast Cancer Conference (EBCC) in Florence in 1998 called for multidisciplinary breast therapy units, the conditional and quality assurance requirements for so-called "breast units" (BU) have been defined [44]. A working group of the European Organization for the Research and Treatment of Cancer (EORTC) and the European Society of Mastology (EUSOMA) has developed basic requirements for breast cancer specialists, which made the quality assurance control of specialist care possible [45]. The European Union of Medical Specialists (UEMS) and the European Society of Surgical Oncology (ESSO) established a breast surgery licensing exam in 2010, in which the National Institute of Oncology (NIO) has been actively involved for years. At the second EBCC, the "Brussels Statement" established a set of accreditation criteria [46]. In 2019, ESSO, UEMS, the European Breast Cancer Coalition (Europa Donna), the European School of Oncology (ESO), the European Breast Cancer Research Association of Surgical Trialists (EUBREAST), the European Commission Initiative on Breast Cancer (ECIBC), the Hungarian-initiated Central-Eastern European Breast Cancer Surgical Consortium (CEEBCSC) and the Group for Reconstructive and Therapeutic Advancements (G.Re.T.A.) launched the Breast Surgical Oncology (BRESO) project [47]. The BRESO project has developed a continent-wide standardized breast surgery curriculum and quality assurance system and its accreditation requirements. As a result of these statements, the European Parliament issued a resolution in 2003 clearly supporting the extension of the institutional system of qualified BUs in Europe, and in 2013 a summary of the minimum requirements for Breast Centres was published [48].

The requirement for accredited BU certification is that in the given centre at least 150 newly diagnosed breast cancer patients receive complex oncological treatment per year based on decisions of the multidisciplinary breast therapy committee, according to continuously updated professional protocols. An essential part of accreditation is the development and maintenance of a standardized database, the provision of population mammography screening programmes and the provision of educational and other scientific research activities [48-50]. The domestic situation and results of the BU system in Hungary was reported by our working group in the Orvosi Hetilap in 2016 [51].

As a consequence of the rapid spread of modern oncoplastic breast surgery in the recent decades, not only the removal of the breast tumour, but also the aesthetically complete preservation or post-mastectomy reconstruction of breasts is now an essential part of the surgical care [52-54]. In the absence of contraindications, any woman with breast cancer undergoing mastectomy should be offered and provided with the possibility of breast reconstruction [55]. The resulting demand for breast reconstruction not only poses a challenge for breast and plastic surgeons, but also raises a number of systemic issues in all European countries.

Beside the basic reconstructive surgical procedures, however, additional indications and breast surgeries arising from the oncoplastic activity are awaiting clarification and regulation. The evaluation and controlled implementation of these extra procedures also contain a number of unknown factors even for the currently developed breast surgical care systems.

The primary system-level breast reconstruction on wide population significantly expands the secondary tasks. As a result, new issues arise, which mean further load for the health care system: aesthetic changes of the reconstructed or contralateral symmetrized breast due to weight gain known to occur as a result of long term (5-10 year long) endocrine treatment [56-58], “aging” secondary to the excellent survival [59-61] or fibrosis after the oncological treatments (e.g. RT) [62].

Beyond the above mentioned expectations, to determine the optimal volume of human resources and surgical capacity of the health care system, complications due to technical problems (e.g. implant rupture) or conditions (e.g. capsular contracture) of implants and the issue of the mass occurrence of further possible surgical corrections resulting from changes in contralateral breast symmetry should also be taken into account.

Taking into consideration all the professional aspects, targeted aesthetic goal and the optimal and maximum number of reconstructive surgeries that can be performed within the framework of the oncology care system has to be determined. Oncoplastic care, as standard breast cancer surgical care, includes subjective indications or possible corrections for life-long cosmetic changes that go beyond primary oncology and reconstructive surgery and are often difficult to determine professionally.

Understanding, scientifically based identification and realistic assessment of new breast surgery needs is an essential basis for evolving the necessary set of conditions. At present, the National Health Insurance Fund of Hungary (Nemzeti Egészségbiztosítási Alapkezelő, NEAK) finances the reconstruction of the removed breast for all Hungarian insured persons, however, these complex new indications are currently not recognized at the system-level and are not managed accordingly. Breast reconstruction is a significant achievement for Hungarian breast cancer patients, but with the increase in the need for reconstruction and an expansion of the range of indications, an avalanche-like, unregulated situation may develop, the prevention of which requires professional knowledge and planning.

2. AIMS OF THE THESIS

1. Assess relationship between the clinicopathological characteristic, the molecular genetical subtype and location by quadrants of the breast cancer and the subregions of the axilla and thus describe a functional and morphologic lymphatic drainage pattern

2. Assess the coverage of the axillary volumes by standard and high tangential fields (STgF and HTgF) for whole breast irradiation (WBI)

3. Assess the SLN positivity rate in the lateral, undissected subregion when the ARM technique is applied

4. Analyse the oncological and cosmetic importance of the NAC versus its components, the nipple and the pigmented skin of the areola

5. Assess the opinions and needs of the Hungarian breast cancer population about a modern oncoplastic health care system

3. PATIENTS AND METHODS

3.1. The retrospective cohort study of the mapping of the functional anatomy of lymphatic drainage to the axilla in early breast cancer.

This study - registered on Clinicaltrials.gov (identifier: NCT01804309) and approved by the institutional ethical committee board - was performed between March 2013 and February 2015 at the NIO, Hungary. 933 female patients older than 18 years were enrolled with primary unilateral invasive or microinvasive, clinically lymph node-negative early-stage breast cancer (clinically T≤5 cm, N0M0). Exclusion criteria included previous ALND, cN1-2, pregnancy, lactation and necessity of neoadjuvant treatment for breast cancer [63, 64].

SLNB technique

The complex oncological therapy was performed according to the actual international guidelines [63-65] adopted by the NIO and was not different from those who were not included in the trial. Radiopharmaceutical (80 Mbq 99m Tc labelled nanocolloid, particle size: 50-800 nm) was injected to the intratumoural area or periareolar tissue on the day before surgery. If the lymphoscintigraphy was unsuccessful, 2-3 ml of periareolar Patent blue 25 mg/ml® dye injection was applied 10 minutes before the operation.

Patients then underwent a wide excision or mastectomy and axillary SLNB followed by ALND instantly if the SLN was positive by intraoperative imprint cytology or as a second operation if the SLN was positive only by histological examination. If isolated tumour cells or micrometastases were found in the SLN (n=33), ALND was omitted.

The subregional localisation of the SLN(s) was identified and recorded on a standardised data sheet by the operating surgeons immediately after biopsy in the operating theatre (Figure 1). The harvested SLNs were separated and labelled with their localisation for pathological processing. Imprint cytology was performed intraoperatively, and if the result was positive, the operation was completed with ALND. Postoperatively, all the removed lymph nodes were meticulously examined by the pathologists according to the guidelines [66, 67]. In cases of false negative SLNB, the subregional localisation and the number of metastatic lymph nodes left behind in the axilla could not be identified by our applied methods.

RT and coverage simulation

Following BCS, all patients had 3D-conformal RT. Patients were placed supine with both arms up and both hands holding on to a support during CT simulation. CT scan images with 5-mm sections were obtained. The breast was irradiated with two opposing tangential fields with 6 MV photons. STgF margins were determined by palpation of the breast parenchyma with the addition of a 1-2-cm margin in all directions. The superior borders of these fields intended to treat the breast only, without regard to nodal coverage. Approximately 2 cm (max. 3 cm) of the lung was included in the posterior aspect of the field. In node-positive patients, an additional field was also used to deliver an effective dose to the axillary apex and clavicular fossa. The total dose of the whole breast and supraclavicular fossa was 50 Gy (25x2 Gy). Breast irradiation was given via STgFs. The STgF upper margin was generally the base (± 1 cm) of the clavicle. Retrospectively, for the purpose of this study in 61 randomly selected node-positive patients treated with breast-conserving therapy in whom the SLNs were found in the anterior or posterior axillary subregions (Level I), HTgFs were simulated using the same CT data. HTgF consisted of a superior border placed at the inferior edge (or below maximum 2 cm) of the humeral head. Before RT planning, axillary volumes (Levels I, II and III) were contoured using the Radiation Therapy Oncology Group (RTOG) contouring atlas [68]. Coverage of the axillary volumes by tangential fields was classified according to the tangential field-planning target volumes (Levels I, II and III) overlap: 100% overlap (complete coverage), <100% overlap (partial coverage), and 0% overlap (lack of coverage: out of field). Examples of coverages are given in Figure 2.

Statistical analysis

All the collected data were registered in the institutional database and statistically analysed using Fisher's exact test. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed using Statistica 12.0 software (StatSoft, Tulsa, OK) or PAST version 1.86b [69].

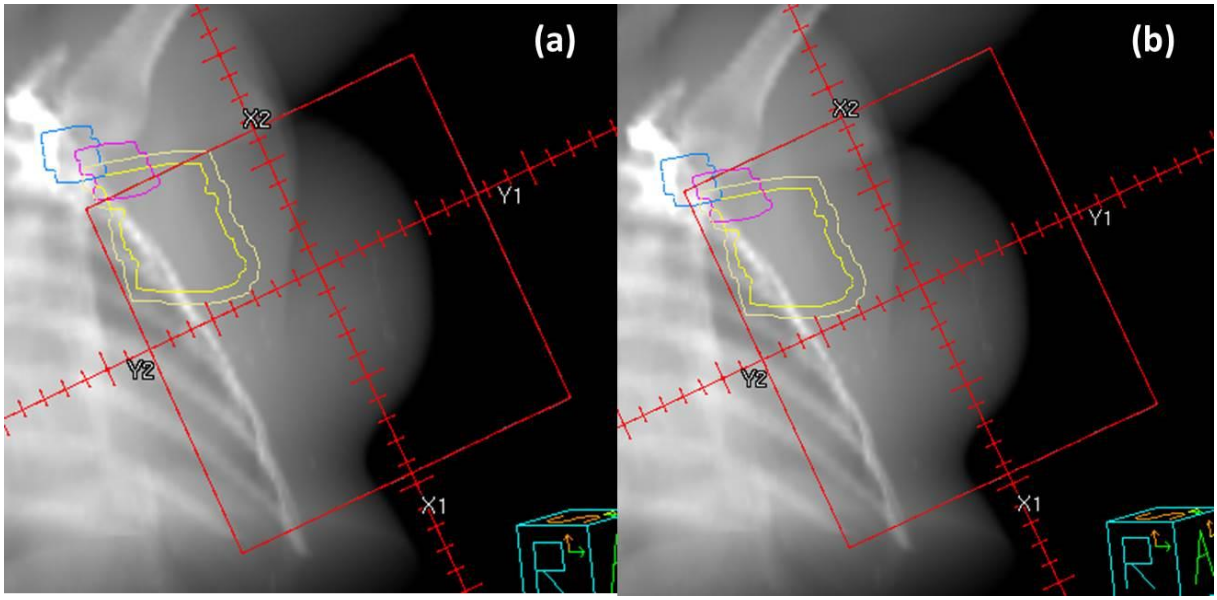

Figure 2.

(a) Coverage with standard tangential field (red square). Yellow lines = Level I volumes: inner line - clinical target volume; outer line - planning target volume; partial coverage. Purple line = Level II clinical target volume; partial coverage. Blue line = Level III clinical target volume; no coverage, out of field

(b) Coverage with high tangential field (red square). Yellow lines = Level I volumes: inner line - clinical target volume; outer line - planning target volume; complete coverage. Purple line = Level II clinical target volume; partial coverage. Blue line = Level III clinical target volume; partial coverage

3.2. The comparative study of areola-sparing mastectomies versus nipple-sparing mastectomies to analyse of the oncological and cosmetic importance of the components of the nipple-areola complex

This single-centre retrospective comparative study was performed between April 2013 and December 2018 at NIO, based on the prospectively led institutional database. The study was approved by the institutional ethics committee board and involved a total of 251 female patients (ASM (n=147) or NSM (n=104)).

The diagnosis of breast cancer, additional staging examinations, adjuvant treatments, and follow-ups were performed according to an institutional protocol based on the European

Society of Medical Oncology (ESMO) and on the European Society for Radiotherapy and Oncology (ESTRO) guidelines [64, 70, 71].

The indication for mastectomy was either therapeutic for breast cancer or prophylactic for patients with BRCA mutation. Both ASM and NSM operations were performed with exactly the same indications as those used for therapeutic procedures: based on the actual guidelines, ASM was the technique first applied at our department, while it was subsequently replaced in our daily practice by NSM after its international acceptance [41, 43].

Surgical technique

All the procedures in both groups were performed by the same qualified breast surgeons (European Board of Surgery Qualification, (EBSQ)) based on the decisions of the breast multidisciplinary team with exactly the same delayed-immediate implant-based breast reconstruction techniques [72].

In the case of ASM, the whole mammary gland was dissected in a standardized way with an electrosurgical device using an infero-lateral incision. After the complete mobilization of the glandular tissue from the chest wall muscles and the subcutaneous tissue along the superficial fascia, a circumferential incision was made around the nipple base allowing the complete excision of the mammary gland with the nipple attached to the breast tissue. The major pectoral and serratus anterior muscles were dissected and elevated from the chest wall, and a Mentor Smooth Round Tissue Expander with a remote injection valve (size 400 – 550 – 700 ml) was placed and inflated (to an average of 40 ml) in the previously prepared sub-muscular pocket. After the closure of the submuscular pocket by stitching to the lateral edge of major pectoral and serratus anterior muscles, the subcutaneous and skin layers were closed with continuous subcutaneous and intradermal sutures. The expander implant was gradually inflated during the routine follow-up visits. The expander implant replacement with permanent implants and the contralateral symmetrisation was performed 3-14 months later depending on the completion time of the adjuvant treatments. The nipple was reconstructed using local flaps as an outpatient procedure after an additional 3-9 months.

For NSM, the same infero-lateral incision and standardized dissection technique was applied. To assess the surgical margins below the NAC, after the excision of the mammary gland, a biopsy (“coring”) was taken from the posterior aspect of the nipple and was sent as a

separate specimen for postoperative histological analysis. If the pathological examination of that intramamillary tissue sample or the removed mammary gland, in the case of ASM, was positive, the NAC was excised, and the patients (ASM: n=2; NSM: n=3) were excluded from the study. If the surgical margin was clear, the nipple was spared followed by breast reconstruction with a submuscular expander implant and the implant was replaced and symmetrisation was performed later as described above.

Treatment of axilla and RT

For the axillary staging SLNB was performed. After 1 January 2015, axillary clearance was omitted in patients with limited axillary metastases, according to the criteria of the ACOSOG Z0011 trial [24, 25]. In selected cases, patients with metastatic axillary SLN were treated with axillary and supraclavicular RT.

Postmastectomy radiotherapy (PMRT) in node-positive patients was always recommended for high-risk patients with one to three positive axillary lymph nodes, furthermore involved resection margins, four or more involved axillary lymph nodes and T3–T4 tumours independent of the nodal status [64, 71]. Doses used for local and/or regional adjuvant irradiation were 50 Gy in 25 fractions of 2.0 Gy.

Assessment of complications, aesthetic outcomes and quality of life

Postoperative complications were assessed by applying the Clavien-Dindo classification system [73, 74]. Minor, asymptomatic complications (e.g., infections, haematomas or suffusions, seromas, partial skin/NAC necrosis, rippling, wound dehiscence and lymphedema (redness of the skin)) without need for medical therapy or surgical intervention were considered Grade I, while the same complications treated with antibiotics or minor interventions (e.g., suture of wound dehiscence, chronic seroma puncture) were considered Grade II complications. Any complications (e.g., haematoma, chronic infections, full thickness skin/NAC necrosis, implant loss and wound dehiscence) requiring invasive surgical procedures were classified as Grade III. Life-threatening complications or patient death were categorized as Grade IV and V complications, respectively.

For the assessment of the aesthetic outcomes, a 5-point Likert scale (score: 1, strongly disagree; 2, disagree; 3, undecided; 4, agree; 5, strongly agree) was applied [75]. The evaluation was performed by a committee of 3 breast surgeons (who were not involved in the surgical

procedure) by reviewing the whole series of photo documentation and individually scoring each patient six months after the operation.

The BREAST-Q validated patient-reported outcome measure (PROM) reconstruction module version 2.0 postoperative questionnaire was applied to measure the quality of life (QoL) of the patients [76]. Selected scales were used to measure satisfaction with the breast and psychosocial, physical and sexual wellbeing. The BREAST-Q questionnaire was administered to the patients 6 months after surgery. The patients' responses to each item on the scale were transformed using a scoring conversation table. The results ranged from 0-100, with higher scores reflecting higher satisfaction or better QoL.

All the collected data were registered in the institutional database and statistically analysed [69]. P-values less than 0.05 were considered statistically significant.

3.3. The questionnaire study of evaluation of the needs of Hungarian breast cancer patients for modern oncoplastic breast surgical treatment

This study was conducted enrolling 500 patients who underwent mastectomy and the breast reconstruction was either done at the same time as the removal of the primary tumour (immediate) or started (e.g. by implantation of a tissue expander) and completed in the second session (delayed-immediate breast reconstruction) between January 2015 and December 2017 at the NIO. The study and the questionnaire was approved by the institutional ethical committee board and does not infringe the requirements of the Declaration of Helsinki and Tokyo [77].

The diagnosis of breast cancer, additional staging examinations, adjuvant treatments and follow-ups were performed according to the current international guidelines applied by the NIO [71, 78, 79]. The operations were performed by experienced and internationally qualified breast surgeons (EBSQ) and plastic surgeons based on the decisions of the institutional multidisciplinary team.

Questionnaires were distributed to patients the day before breast surgery and were completed voluntarily and anonymously prior to the intervention.

Following questions on age, highest level of education, and marital status, the questionnaire contained eleven structured questions to measure the emotional and mental

condition and attitudes related to the loss and reconstruction of breast, the expectation of cosmetic outcome, the qualification of the operating surgeon and the demands for the health care system and funding (Table 1).

The answers and their social context was statistically analysed using Fisher's exact and Chi-squared tests [69]. P-values less than 0.05 were considered statistically significant.

Table 1. *A structured questionnaire of the survey of the oncoplastic care and the answers received*

1. How much are you disturbed by breast loss and its aesthetic deformity on a scale of 1-10?? (1-no disturbance - 10-terrible disturbance)			
n	mean	median	standard deviation (SD)
495	8	9	3
missing data = 5 (1%)			
2. When do you undergo breast reconstruction?			
Months or years after tumour removal		Simultaneously with tumour removal	
167 (33%)		307 (61%)	
missing data = 26 (5%)			
3. What you realistically expect from breast reconstruction?			
"some kind" of breast	a pretty décolletage in brassiere	more beautiful breast, than before	perfect breasts
46 (9%)	194 (39%)	140 (28%)	99 (20%)
missing data = 21 (4%)			
4. To what extent can you realistically accept symmetry at the end of breast reconstruction?			
My natural breasts were not symmetrical either, so it does not matter if my reconstructed breasts are not the same	Let my reconstructed breasts be roughly the same in a dress or brassiere	Let my reconstructed breasts be pretty much the same naked	Only perfect symmetry is acceptable for me
12 (2%)	105 (21%)	348 (70%)	32 (6%)
missing data = 3 (1%)			
5. How many surgeries under general anaesthesia would you take maximally to have your breast reconstructed?			
Maximum two	Maximum 3 to 4	Maximum 5 to 6	Any
217 (43%)	184 (37%)	25 (5%)	67 (13%)
missing data = 7 (1%)			

6. In your opinion, how many "state-funded" reconstructive procedure is appropriate for an insured patient, known that sources are not endless?		
Maximum two	Maximum 3 to 4	Any
107 (21%)	220 (44%)	157 (31%)
missing data = 16 (3%)		

7. What is your opinion regarding the change of your reconstructed breast over time (by aging)?		
Does not need further surgery, because it is a natural process	It is a natural process, that will be an individual aesthetic issue	Even decades later, I consider it reconstructive surgery and not aesthetic surgery
71 (14%)	275 (55%)	139 (28%)
missing data = 15 (3%)		

8. Would you agree to have your breast reconstruction performed by a general surgeon instead of a plastic surgeon?	
Yes	No
40 (8%)	448 (90%)
missing data = 12 (2%)	

9. In your opinion, who should perform the modern surgical procedures of breast cancer treatment (oncoplastic surgery, breast reconstruction) in Hungary?			
General surgeon, as usually in our country	Gynaecologist, as sometimes in our country	Plastic surgeon	Specially trained breast surgeon with the involvement plastic surgeon, if needed
5 (1%)	3 (1%)	54 (11%)	430 (86%)
missing data = 8 (2%)			

10. In your opinion, how acceptable is it that in Hungary, in the 21st century, only one or two hospitals have specially prepared, modern breast surgical centres / units?			
As good as it is now	It's unfortunate, but that's it	It is very unfortunate, but who wants better goes to private care	Unacceptable, modern specialized breast surgery should be provided
2 (1%)	51 (10%)	46 (9%)	394 (79%)
missing data = 7 (1%)			

11. Do you think that being operated by a breast surgeon has a significant effect on your recovery?			
Does not affect	Affects	Strongly affects	One of the most important
14 (3%)	54 (11%)	111 (22%)	316 (63%)
missing data = 5 (1%)			

4. RESULTS

4.1. The retrospective cohort study of the mapping of the functional anatomy of lymphatic drainage to the axilla in early breast cancer

A total of 933 women were enrolled in the study. The mean age of the patients was 64.1 years (range 19 to 91 years, median: 64 years). Three women were excluded because the breast tumour was larger than 5 cm according to the postoperative pathologic examination. Another two patients were ruled out due to newly discovered lympho-proliferative disorders affecting the axillary lymph nodes. Another 58 patients were discarded because of an uninterpretable sentinel data sheet or incomplete clinical-histological data.

The detailed pathologic characteristics of the primary breast tumours are summarised in Table 2.

Table 2. *Pathological characteristics of the primary breast tumour*

pT	**n**	**%**
pTis	104	11.8
pT1mi	3	0.3
pT1a	31	3.5
PT1b	95	10.8
pT1c	316	36.0
pT2	300	34.1
pT3	30	3.4
Grade (invasive tumours)		
I	180	23.4
II	370	48.1
III	219	28.5
Grade (in situ carcinomas)		
Low	28	26.9
Medium	50	47.8
High	26	25.3
Receptor status		
ER	751	80.5
PR	641	68.7
Her2	72	7.7
Molecular subtype		
Luminal A	438	59.4
Luminal B	171	23.2
Luminal B-Her2+	41	5.6
Non-luminal	73	9.9
Triple negative	14	1.9

Lymphovascular invasion		
Present	322	39.3
Not present	497	60.7
Histological type		
Invasive ductal carcinoma	643	73.1
Invasive lobular carcinoma	99	11.3
Other invasive	34	3.9
DCIS	75	8.5
LCIS	16	1.8
Other in situ	13	1.5
Palpability		
Palpable	499	55.9
Not palpable	393	44.1
Mitotic activity		
<11	539	67.0
11-20	157	19.5
20<	109	13.5
Type of breast surgery		
Mastectomy	371	39.8
Breast conserving surgery	562	60.2
SLN positivity		
SLN-negative patients	744	79.7
SLN-positive patients	189	20.3
Total removed SLNs	1538	-
SLNs removed per operation	1.6	-
ALND		
Total number of ALND	156	16.7
Total number of removed lymph nodes	2109	-
Lymph nodes removed per ALND	13.5	-
Positive lymph nodes per ALND	406	19.3

Regarding the location of the breast cancer, 44.7% (n=417) were in the upper-outer, 14.7% (n=137) in the upper-inner, 9.9% (n=93) in the lower-outer, 6.7% (n=63) in the lower-inner quadrant, and 2.8% (n=27) in the axillary process (tail of Spence); 12.8% (n=119) were central tumours and 3.5% (n=33) were multiplex.

There was a significant correlation between the location and the molecular subtype of the tumour (p=0.022). Non-luminal tumours were mainly localised in the upper quadrants (84.6% n=11). Similarly, the triple negative subtype was also likely to appear in the upper-outer quadrant (57.1%; n=40). However, cancers in the lower-inner quadrant were mostly Her2-enriched (17.1%; n=7). (Table 3.)

Table 3. *Correlation between molecular subtype (column) and the location (row) of the primary breast tumour (p=0.022)*

	Luminal A		**Luminal B**		**LumB – Her2**		**Non-luminal**		**Triple negative**	
	n	%	n	%	n	%	n	%	n	%
Upper-outer	210	49.3	73	44.0	18	43.9	7	53.9	40	57.1
Upper-inner	65	15.3	39	23.5	5	12.2	4	30.8	9	12.9
Lower-outer	47	11.0	20	12.1	4	9.8	0	0	9	12.9
Lower-inner	36	8.5	13	7.8	7	17.1	0	0	1	1.4
Central	62	14.6	17	10.2	7	17.1	2	15.4	6	8.6
Axillary process	6	1.4	4	2.4	0	0	0	0	5	7.1

The tracer for lympho-scintigraphy was injected intratumourally and periareolarly in 38.8% (n=362) and 57.6% (n=537) of the cases, respectively. We used only radiopharmaceutical (80 Mbq 99m Tc labelled nanocolloid) in 86.9% (n=811), Patent blue dye in 4.4% (n=41) and both in 4.8% (n=45) of the cases.

None of the examined characteristics of the primary breast cancer (molecular subtype p=0.360) had significant correlation with the subregional localisation of the SLN.

We divided our study population into two groups based on the injection site and analysed the relationships between the location of the SLN and location of the primary breast tumour. In case of intratumoural application, we found significant correlation between the location of the breast cancer and the subregional location of the SLN (p=0.016). However, examining only the histologically positive SLNs, the relationship between their location and the primary tumour location was not statistically significant (p=0.674).

If periareolar injections were used, the location of the SLN was not dependent on the location of the primary breast tumour (p=0.398), whilst the correlation between the location of the positive SLN and the location of the breast cancer was statistically significant (p=0.039). (Table 4.)

According to our data, tumours in the upper-outer quadrant are most frequently drained to the anterior subregion (34.2%). Posterior subregion receives lymph mainly from the upper-outer quadrant (31.6%) and the axillary process (36.3%), whereas the inner and central quadrants have very similar drainage patterns with a tendency to give efferent lymphatics more often to the anterior (53.9%, 69.6% and 54.5%) and central (28.8%, 26.1% and 22.7%) lymph

nodes. The central lymph nodes receive lymphatic drainage equally from the different quadrants of the breast. (Table 4.)

An average of 1.6 (range: 1-8, median: 1) SLNs were harvested per operation, and the SLN positivity rate was 20.3% (n=189).

We also analysed the distribution pattern and metastatic status of the SLN in the subregions of the axilla (Table 4.). The most common site of the SLN was the anterior subregion (39.9%; n=349), while the least common was the apical subregion (3.4%; n=30). In contrast, the positivity rate was higher in the apical subregion (30.0%; n=9) than in the anterior subregion (20.9%; n=73). The SLN was present in the lateral subregion in 5.5% (n=48) of the cases. Of these 48 lymph nodes, 11 SLNs - 1.3% of the total cases - were positive. In the central and posterior subregions, 53 (6.1%) and 43 (4.9%) SLNs, respectively, were found to be positive out of the 245 (28.0%) and 203 (23.2%) removed lymph nodes, respectively.

In 91.1% (n=797) of the cases, the SLN appeared in the anterior, posterior or central subregions, corresponding to Level I and II zones (Table 4).

Table 4. *Correlation between the location of the primary breast tumour (column) and the subregional location of the SLN (row) if intratumoural injections were used (p=0.016) and distribution pattern and metastatic status of the SLN in the subregions of the axilla*

	Upper outer	**Lower outer**	**Upper inner**	**Lower inner**	**Central**	**Axillary process**	**Stained & removed SLN**	**Positive SLN**	**Positivity rate**
anterior	65 (34.2%)	13 (41.9%)	28 (53.9%)	16 (69.6%)	12 (54.5%)	5 (45.5%)	349 (39.9%)	73	20.9%
central	55 (28.9%)	8 (25.8%)	15 (28.8%)	6 (26.1%)	5 (22.7%)	1 (9.1%)	245 (28.0%)	53	21.6%
posterior	60 (31.6%)	7 (22.6%)	6 (11.5%)	1 (4.3%)	2 (9.1%)	4 (36.3%)	203 (23.2%)	43	21.2%
lateral	6 (3.2%)	3 (9.7%)	3 (5.8%)	0 (0.0%)	1 (4.6%)	1 (9.1%)	48 (5.5%)	11	22.9%
apical	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	30 (3.4%)	9	30.0%

In 503 patients, the SLN was located within the anterior or posterior subregion (Level I). 111 of them (22.1%) had axillary lymph node metastasis, and 83 (16.5%) of them were

treated with RT in our Institute. Sixty-one women were subjected to WBI. The coverage of axillary volumes by tangential fields is given in Table 5. There was a significant difference between the two plans regarding the coverage of the Level I axillary volume. HTgF increased the rate of complete coverage from 0% to 65.6% (40 of 61; p<0.0001). Concerning the Level II volume, the rate of complete coverage with STgF or HTgF was 0% and 6.6% (4 of 61), respectively (p=0.1198). The rate of "out of field" cases was very high with STgF, 72.1% (44 of 61), but "out of field" cases were not observed with HTgF irradiation (p<0.0001). The coverage of the Level III volume was very poor (rate of "out of field" with STgF or HTgF: 91.8% and 9.8%, p<0.0001).

Table 5. *Coverage of axillary volumes by tangential fields (n=61)*

% (No.)		**STgF**	**HTgF**	**p-value**
Level I	Complete	0 (0)	65.6 (40)	< 0.0001
	Partial	100.0 (61)	34.4 (21)	-
	Out of field	0 (0)	0 (0)	-
Level II	Complete	0 (0)	6.6 (4)	0.1198
	Partial	27.9 (17)	93.4 (57)	-
	Out of field	72.1 (44)	0 (0)	< 0.0001
Level III	Complete	0 (0)	0 (0)	-
	Partial	8.2 (5)	90.2 (55)	-
	Out of field	91.8 (56)	9.8 (6)	< 0.0001

4.2. The comparative study of areola-sparing mastectomies versus nipple-sparing mastectomies to analyse of the oncological and cosmetic importance of the components of the nipple-areola complex

Eight patients were excluded from the study due to lost follow-up or incomplete clinicopathological data; eleven women from both groups were excluded because of previous breast surgery, and five patients (ASM: n=2; NSM: n=3) were omitted from further evaluation because of positive nipple-areola margins requiring NAC resection. As a result, a total of 134 and 93 patients were enrolled and underwent ASM and NSM, respectively.

Detailed patients and tumour characteristics are summarized in Table 6 and Table 7, respectively.

***Table 6**. Patient characteristics of the ASM and NSM groups.*

	ASM	**NSM**	**p**
Number of patients	**134**	**93**	
Age (years)			
median (min. – max.)	41 (26 – 64)	40 (26 – 70)	0.365
BMI (kg/m^2)			
mean ± SD	21.6 ± 3.1	21.2 ± 3.4	0.285
Cup size	**n (%)**	**n (%)**	
A	23 (17.2)	7 (7.5)	0.003
B	75 (55.9)	62 (66.7)	
C	25 (18.7)	24 (25.8)	
D	11 (8.2)	0 (0.0)	
Indication	**n (%)**	**n (%)**	
therapeutic	89 (66.4)	85 (91.4)	$1.2x10^{-5}$
prophylactic	45 (33.6)	8 (8.6)	
Operative duration (minutes)			
median (min. – max.)	80 (50 – 150)	76 (43 – 120)	0.431
Neoadjuvant	**n (%)**	**n (%)**	
chemotherapy	20 (22.5)	9 (10.6)	0.244
Initiation of adjuvant therapy (weeks)			
median (min. – max.)	7.4 (4.6 – 11.9)	8.1 (4.1 – 12.0)	0.124
Adjuvant	**n (%)**	**n (%)**	
Chemotherapy/Biological therapy yes no not reported	 34 (25.4) 59 (44.0) 41 (30.6)	 19 (20.4) 61 (65.6) 13 (14.0)	0.068
Radiotherapy yes no not reported	 32 (23.9) 63 (47.0) 39 (29.1)	 27 (29.0) 53 (57.0) 13 (14.0)	0.993
Endocrine therapy yes no not reported	 46 (34.3) 45 (33.6) 43 (32.1)	 61 (65.6) 21 (22.6) 11 (11.8)	0.001

There was no significant difference in duration of the surgical procedures between the two groups (p=0.431). The median time of ASM was 80 minutes (range: 50-150 minutes), while the NSM operations lasted for 76 minutes (range: 43-120 minutes) on average (Table 6).

Table 7. *Characteristics of the primary breast tumour and regional lymph nodes in the ASM and NSM groups*

	ASM	**NSM**	**p**
Pathological TNM	**n= 89 (therapeutic)**	**n=85 (therapeutic)**	
pT	**n (%)**	**n (%)**	0.026
pTis	5 (5.6)	6 (7.1)	
pT1	37 (41.6)	33 (38.8)	
pT2	23 (25.8)	19 (22.3)	
pT3	4 (4.5)	18 (21.1)	
pN	**n (%)**	**n (%)**	0.900
pN0	47 (52.8)	53 (62.3)	
pN1	18 (20.2)	19 (22.3)	
pN2	3 (3.4)	2 (2.4)	
pN3	1 (1.1)	2 (2.4)	
ypT	**n (%)**	**n (%)**	
ypT0	5 (5.6)	4 (4.7)	
ypT1	9 (10.2)	2 (2.4)	
ypN2	4 (4.5)	2 (2.4)	
ypN3	2 (2.2)	1 (1.2)	
ypN	**n (%)**	**n (%)**	
ypN0	11 (12.4)	6 (7.0)	
ypN1	7 (7.9)	2 (2.4)	
ypN2	1 (1.1)	0 (0)	
ypN3	1 (1.1)	1 (1.2)	

Grade (invasive breast cancer)			0.435
I	16 (18.0)	11 (12.9)	
II	34 (38.2)	40 (47.1)	
III	39 (43.8)	34 (40.0)	
Receptor status			
ER positive negative not reported	 60 (44.8) 32 (23.9) 42 (31.3)	 59 (63.4) 10 (10.8) 24 (25.8)	0.004
PR positive negative not reported	 56 (41.8) 35 (26.1) 43 (32.1)	 56 (60.2) 13 (14.0) 24 (25.8)	0.008
Her2 positive negative not reported	 20 (14.9) 71 (53.0) 43 (32.1)	 15 (16.1) 52 (55.9) 26 (28.0)	0.951
Histological type			
Invasive ductal carcinoma	74 (83.2)	60 (70.6)	0.349
Invasive lobular carcinoma	5 (5.6)	11 (12.9)	
Other invasive	4 (4.5)	6 (7.1)	
DCIS	5 (5.6)	6 (7.1)	
LCIS	1 (1.1)	2 (2.3)	
Nipple – tumour distance (cm)			
median (min. – max.)	2.7 (0.6 – 7.0)	3.1 (0.7 – 7.0)	0.497
Follow-up 45 months (range: 20.1-82.7)			
local recurrence	3 (3.4)	2 (2.4)	
distant metastatic disease	5 (5.6)	1 (1.2)	
distant metastases-related death	2 (2.2)	1 (1.2)	
Axillary surgery			0.656
Sentinel lymph node biopsy	64 (71.9)	62 (72.9)	
Axillary lymph node dissection	23 (25.9)	19 (22.4)	
No axillary surgery	2 (2.2)	0	
Not reported	0	4 (4.7)	

The recorded early postoperative complications in the two groups are summarized in Table 8. In total, the overall complication rate was 13.4% (n=18) for ASM and 12.9% (n=12) for NSM. The majority of complications were Grade I, including partial skin/NAC necrosis, seroma, infection or wound dehiscence, which healed spontaneously in both groups.

Table 8. *Early postoperative complications based on the Clavien-Dindo classification in the ASM and NSM groups*

	ASM	**NSM**	**p**
	134 n (%)	**93 n (%)**	
Grade I	**12 (9.0)**	**9 (9.7)**	
infection	4 (3.0)	3 (3.2)	
seroma	2 (1.5)	2 (2.1)	
partial skin / NAC necrosis	3 (2.2)	2 (2.1)	
rippling	2 (1.5)	1 (1.1)	
wound dehiscence	1 (0.7)	1 (1.1)	
Grade II	**3 (2.2)**	**1 (1.1)**	
infection	2 (1.5)	0 (0.0)	
chronic seroma	1 (0.7)	1 (1.1)	
Grade III	**3 (2.2)**	**2 (2.1)**	
haematoma	2 (1.5)	1 (1.1)	
implant loss	1 (0.7)	1 (1.1)	
Overall	**18 (13.4)**	**12 (12.9)**	**0.908**

The mean follow-up period was 45.0 months (range: 20.1-82.7). During the follow-up period three distant metastases-related deaths were recorded (ASM:2.2%, n=2; NSM:1.2%, n=1), five local recurrences were observed in preserved areola or the nipple (ASM:3.4%, n=3; NSM:2.4%, n=2), while overall six distant metastatic diseases were recorded (ASM:5.6%, n=5; NSM:1.2%, n=1). There was no significant difference in DFS (p=0.762) and OS (p=0.601) between the two groups (Figure 3 and 4).

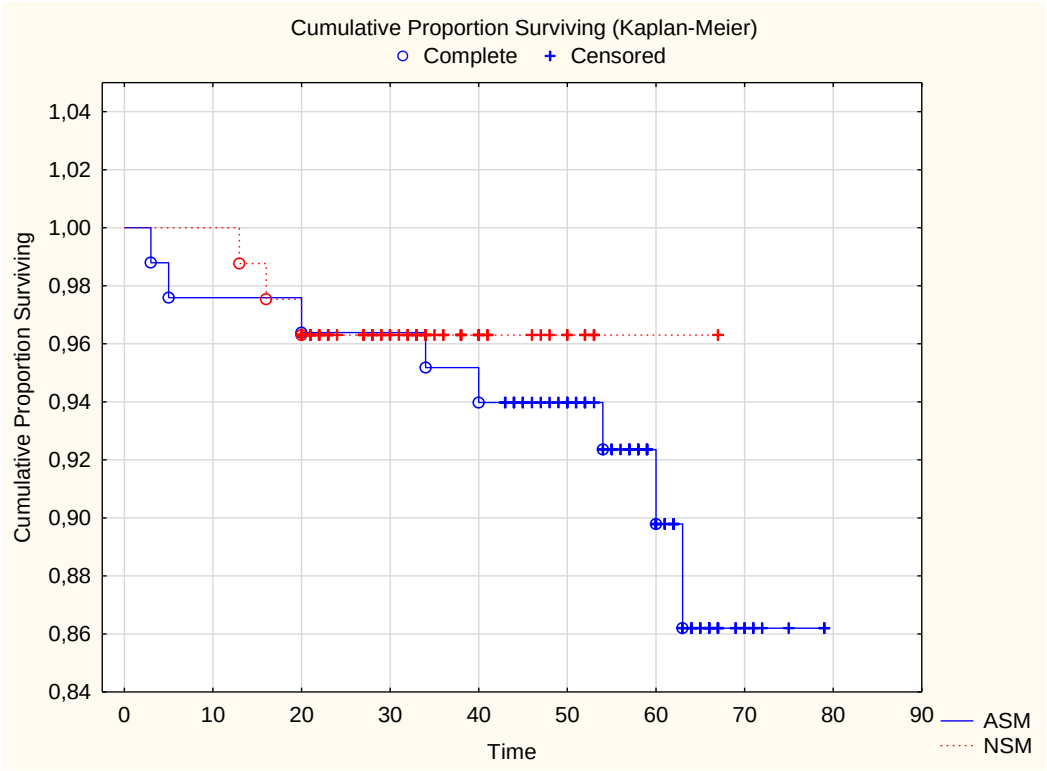

Figure 3. *Kaplan-Meier curve showing DFS of the two groups*

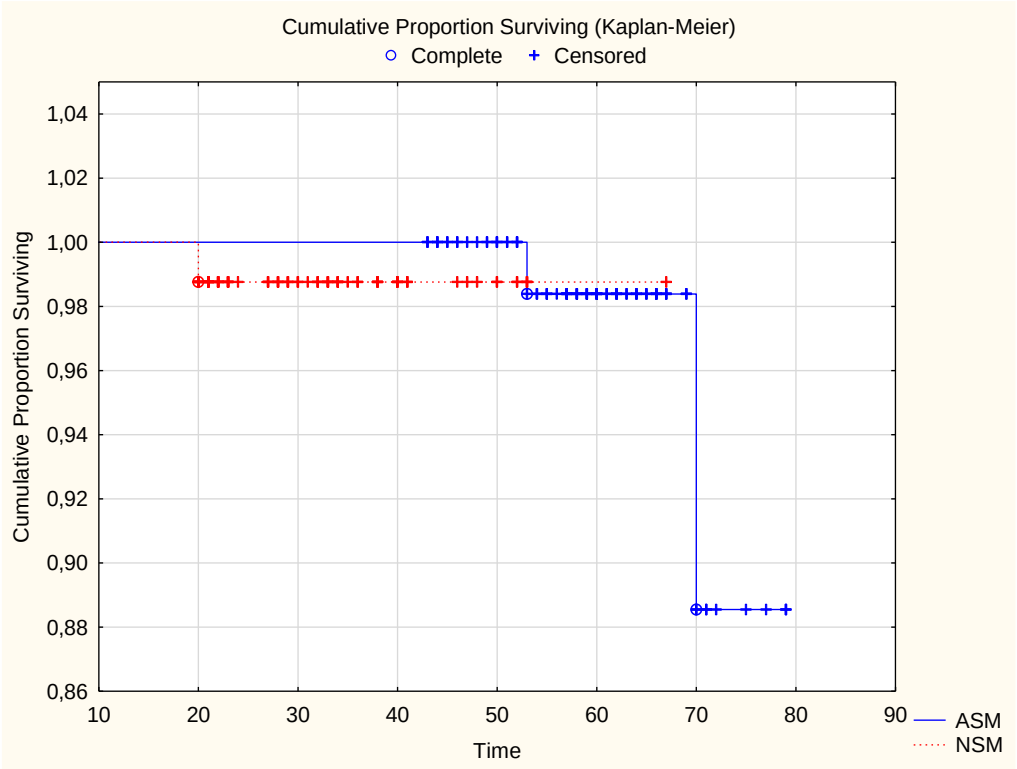

Figure 4. *Kaplan-Meier curve showing OS of the two groups*

The median time until adjuvant treatment initiation was 7.4 weeks (range: 4.6 – 11.9) for ASM and 8.1 weeks (range: 4.1 – 12.0) for the NSM group.

Both groups had the same objective aesthetic outcomes measured by a 5-point Likert scale system. The majority of breast surgeons agreed with the statement that "This patient had an excellent aesthetic outcome", with a median score of 4.1 (range: 2-5) in the ASM group and 4.3 (range: 2-5) in the NSM group.

The results of the corresponding BREAST-Q domains showed no significant difference between ASM and NSM patients (Table 9). The highest mean scores were observed for "physical wellbeing", while the median "satisfaction with breasts" and "psychosocial wellbeing" scores were slightly lower. The lowest mean scores were detected for "sexual wellbeing".

Table 9. *Results of the BREAST-Q postoperative questionnaire*

	ASM mean ± SD	**NSM** mean ± SD	**p**
BREAST-Q postop. 1 - Satisfaction with breasts	64.9 ± 21.2	67.8 ± 17.2	0.691
BREAST-Q postop. 2 - Psychosocial wellbeing	68.4 ± 18.4	72.4 ± 17.5	0.123
BREAST-Q postop. 3 - Physical wellbeing	80.0 ± 14.0	76.5 ± 15.5	0.232
BREAST-Q postop. 4 - Sexual wellbeing	59.1 ± 18.3	54.0 ± 20.9	0.252

4.3. The questionnaire study of evaluation of the needs of Hungarian breast cancer patients for modern oncoplastic breast surgical treatment

The median age of the women was 47 years (min.-max.: 26-73). 52% (n = 260) of those surveyed had a higher education degree and the majority (59%; n = 294) were married. Characteristics of the study population are summarized in Table 10.

Table 10. *Characteristics of the study population*

Age				
n	mean	median	minimum	maximum
485	48	47	26	73
missing data = 15 (3%)				
Highest level of education				
primary school		secondary school		university
7 (1%)		218 (44%)		260 (52%)
missing data = 15 (3%)				
Marital status				
single		married	divorced	widow
52 (10%)		294 (59%)	119 (24%)	20 (4%)
missing data = 15 (3%)				

Understandably, breast loss significantly embarrassed the respondents, with answers averaging 8 ± 3 (mean ± SD) on a scale of 1 to 10; and there was no difference between the responses in terms of education or marital status (Figure 5).

Immediate breast reconstruction was performed in almost two-thirds of cases (61%; n = 307), while in 167 patients (33%), breast reconstruction was delayed-immediate; in the latter case the survey was done months or years after tumour removal, before the final session of the reconstruction.

Based on the answers, 39% (n = 194) of the interviewed women would be satisfied with breasts resulting in a pretty décolletage in brassiere, however, 28% (n = 140) would like to have more beautiful breasts, than the original ones were, and 20% (n = 99) want perfect breasts at the end of the reconstruction process. In terms of expectations, there was a significant correlation with education: higher education was associated with higher expectations ($p < 0.05$). Patients had a firm opinion regarding symmetry, there was no difference in either marital status or education: 70% (n = 348) of women would like roughly identical breasts naked at the end of the reconstruction process.

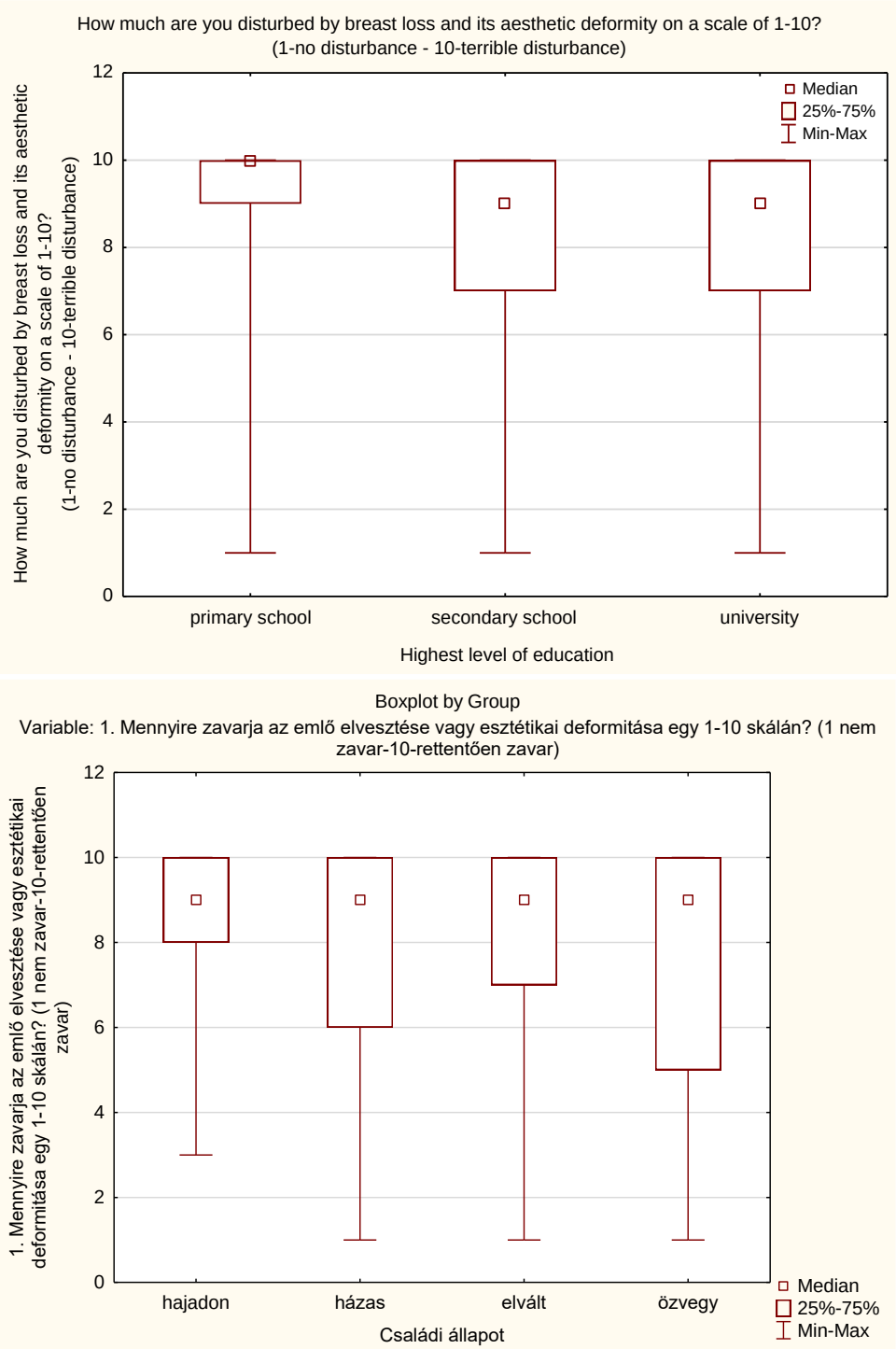

Figure 5. *Evaluation of breast loss by education and marital status (boxplot)*

For an optimal aesthetic outcome, 43% (n = 217) of the survey participants would undertake a maximum of two and 37% (n = 184) up to three or four operations.

The funding of the interventions divided the opinions: according to 44% (n = 220) of the patients, the health insurance company should cover a maximum of three to four operations, 21% (n = 107) think that a maximum of only two surgeries should be funded, while almost a third of the study population (31%; n = 157) are of the opinion that no matter how many interventions are needed, they should all be paid for by the NEAK. Women with a high school education are less likely to justify more surgeries from state funding, while those with a university degree are more likely ($p < 0.05$).

Fifty-five percent of patients (n = 275) believe that age-related changes in reconstructed breasts are an individual aesthetic plastic surgery issue, however, 28% (n = 139) share the opinion that even decades from the primary operation, it will be part of the oncologic reconstructive surgery, not an independent aesthetic surgical procedure.

Patients have a clear view of the surgeon performing the procedure: 90% of them (n = 448) would entrust the reconstruction to a plastic surgeon, moreover, 86% (n = 430) said that modern surgical care for breasts cancer should be performed by specially trained breast surgeons, instead of general surgeons, as currently happens.

The vast majority of respondents (79%; n = 394) do not consider it acceptable that there are currently only one or two certified breast surgical centres in Hungary, whilst 10% (n = 51) accepts the current situation and a further 9% (n = 46) believe that it is necessary to turn to private care for better care.

Almost all of the surveyed women (96%; n = 481) believe that the recovery is significantly influenced by whether breast surgeon performs the operation. Furthermore, 63% (n = 316) think that this is one of the most important factors in regaining their health.

5. DISCUSSION

5.1. Assessing relationship between the quadrants of the breast and the subregions of the axilla and description of the functional and morphologic lymphatic drainage pattern – based on the results of study 4.1.

In summary, we did not find a significant correlation between the histopathological parameters of the primary breast cancer and the subregional location of the SLN. However, it is obvious from the data that the SLN is more than likely to be present in the anterior, posterior and central axillary subregions. Moreover, the SLN positivity rate in the lateral subregion (22.9%; n=11) was not negligible. It is also clear from the data that upper-outer quadrant tumours spread least frequently to the anterior lymph nodes, while inner and central quadrant tumours have similar drainage patterns mainly to the anterior and central subregions.

5.2. Assessing the coverage of the axillary volumes by standard and high tangential fields for whole breast irradiation and axillary reverse mapping - based on the results of study 4.1.

There are several studies concerning the coverage of axillary lymph nodes from whole breast tangential field irradiation. Reed et al. [80] reported that using STgFs, no patient received complete coverage of the axillary Level I–II lymph node volume. They concluded that definitive irradiation of the Level I and II axillary lymph node regions required significant modification of the STgFs. Krasin et al. [81] showed that the use of STgFs does not therapeutically treat the regional lymph nodes. In their series, only 1 out of 25 patients had adequate coverage of the Level I region, and no patient had adequate coverage of Level II. Reznik et al. [82] observed that adequate coverage of Level I, defined when 95% of the volume received 95% of the dose, was achieved in none of the patients with normal tangents and in 6 patients (6 of 35) with high tangents. In a study by Orecchia et al. [83], the Level I nodes were only partially in the STgF, and the mean dose was only 48.7% of the prescribed dose. Our study was performed to address the issue of axillary volume coverage according to tangential field size. We showed that no patient had complete coverage of the Level I or Level II region with STgFs, and in 72.1% of the patients, the Level II volume was completely out of field. Using HTgF, 65.6% of the patients had complete coverage of Level I regions and the complete

coverage rate was only 6.6% for Level II volume. The coverage of Level III region was very poor either with STgF (rate of out of field: 91.8%) or HTgF (rate of out of field: 9.8%).

Our results are consistent with the earlier studies that showed that STgF does not adequately cover the axillary volumes. With modern techniques, adequate coverage of the axillary volumes depends on the cranial field edge. Ohashi et al. [84] used 3D-CRT with a field-in-field technique, and half of the humeral head was inside the field. With this technique, even the dose to the Level III region was appropriate (V90 was 82.8%). In a study by Nagar et al. [85], when the tangential fields were modified to include Level I and II volumes, the mean dose (STgF vs. modified HTgF) increased from 35 Gy to 51 Gy and 11 Gy to 50 Gy, respectively. In patients studied by Belkacemi et al. [86], the STgF was defined with the cranial border set at 2 cm below the humeral head, while the HTgF consisted of a superior border placed at the inferior edge of the humeral head. The mean dose delivered to Level I with STgF or HTgF was 20 Gy and 33 Gy, respectively ($p<0.0001$). We also used classical HTgF such as Belkacemi et al. [86], and the coverage of the Level I region was limited (complete coverage rate 65.6%). Attempts to increase the volume of complete coverage could induce a significant increase in lung dose. Alco et al. [87] suggested shaping the tangential field with multi-leaf collimators according to axillary level volumes to ensure complete coverage, but the inclusion of the axillary region in the target volume increased the irradiated lung volume. Mean lung dose was with the HTgF or multi-leaf collimators HTgF 6.5 and 9.6 Gy, respectively ($p=0.0001$). To study the adequate coverage of the axilla, Levels I, II and III should be defined (delineated) by anatomical structures. STgFs provide limited coverage of the axilla, but HTgFs may provide complete coverage of Level I volume in some patients.

In our study, 9 (1.0%) positive SLNs were in the apical and 11 (1.3%) metastatic lymph nodes were in the lateral subregions. In total, 20 patients with positive lymph nodes (2.3% of our cases) would be left untreated if we applied tangential WBI to treat the axilla.

In our view, for the proper treatment of the axilla, an additional axillary and supraclavicular RT field is needed. This correlates with the findings of the Hungarian OTOASOR prospective randomised clinical trial with axillary and supraclavicular field irradiation in the case of a metastatic SLN without ALND [88].

5.3. Assessing the sentinel lymph node positivity rate in the lateral, undissected subregion when the axillary reverse mapping technique is applied - based on the results of study 4.1

Applying the ARM technique, the lymph nodes stained with blue dye or radioisotope are preserved to prevent postoperative lymphedema. The subregional localisation of the ARM nodes has not yet been clearly identified, but it seems obvious that majority of the lymphatics draining the upper limb traverses deep in the axilla [30]. This was also confirmed by Ikeda et al. [89], who found ARM nodes in zones that correspond to mainly the lateral, apical and posterior axillary subregions.

In our study, 281 (32.1%) SLNs were found within one of these subregions, and 22.4% (n=63) of them were positive. This means that 7.2% of all our cases had one positive lymph node in the expected ARM lymph node regions.

According to these results, due to the high rate of posterior subregional SLN drainage (21.8% n=203) and SLN positivity (21.2%), not only the ALND but also the SLNB carry a high risk of a preserved positive lymph node and have a negative effect on the patient's successful treatment. This corresponds to the results that showed that the oncological safety of the ARM technique in patients with axillary lymph node metastasis from breast cancer is questionable [90, 91], and proper indications, patient selection and further investigations are needed for the safe application of ARM [92].

5.4. Analysing the oncological and cosmetic importance of the nipple-areola complex versus its components, the nipple and the pigmented skin of the areola – based on the results of study 4.2.

In recent years, NSM has become the primary mastectomy technique for prophylactic and therapeutic breast cancer surgical treatment [13]. Several reviews have been published regarding its indications, oncological safety and aesthetic outcomes [40-42]. Tuosimis et al. summarizing the results of three studies with a total of 838 patients, described the ideal candidate for NSM as a patient with A- or B-cup breast size, no ptosis and a BMI < 30 kg/m^2. Regarding their conclusion, the only absolute contraindications were nipple involvement and inflammatory breast cancer [42]. Mallon et al. focused on oncological safety and reported an overall nipple recurrence rate of 0.9% and an overall skin flap recurrence rate of 4.2% [41].

They also examined the complication of nipple necrosis. According to their data, full-thickness necrosis was 2.9%, while partial-thickness nipple necrosis was present in 6.3% of the cases [41]. Headon et al. also assessed the complications by a pooled analysis of 12.358 patients from studies published between 1970 and 2015. They found that the overall complication rate was 22.3% and the nipple necrosis rate was 5.9%. Reviewing 73 studies, Headon et al. reported a pooled locoregional recurrence rate of 2.39% [93]. Regarding aesthetic results, Didier et al.'s questionnaire study found that NSM was significantly better than SSM for body image, satisfaction with nipple appearance and sensitivity and feeling of mutilation [94].

After the international acceptance of NSM in the field of breast cancer surgery, the implementation of SSM has declined significantly. Several papers are analysing the oncological safety, feasibility and possible indications of SSM in breast cancer surgery [40, 95], but significantly less similar studies are available for ASM in the international literature. However as reported by Simmons et al., ASM seems to have similar oncological safety, based on the examined 217 mastectomy specimens. The authors reported areola involvement in only 0.9% (n=2) of the cases [96]. Banerjee et al. obtained exactly the same results and found 2 cases of areola involvement out of 219 mastectomy specimens [97].

The present study did not find significant differences in oncological safety between ASM and NSM. The local recurrence rates were 3.4% (n=3) and 2.4% (n=2) in the ASM and NSM groups, respectively. Significant difference was not proven in DFS (p=0.762) or OS (p=0.601) between the two groups.

Other studies by Simmons et al. examining 17 patients with ASM and immediate breast reconstruction reported one postoperative complication (localized wound infection) and no locoregional recurrence in the 2-year-long follow-up period with excellent aesthetic outcomes superior to those of SSM [95, 98, 99]. The operation times in our study were almost equal (80 and 76 minutes) for both procedures. Moreover, the majority of the complications were minor (Grade I) for both ASM (n=12; 9.0%) and NSM (n=9; 9.7%), while the reoperation rate (Grade III complications) was only 2.2% (n=3) and 2.1% (n=2) for ASM and NSM, respectively. Areola necrosis was present in 2.2% (n=3) of ASM cases, while NAC necrosis was detected in 2.1% (n=2) of NSM cases. Regarding the initiation of adjuvant treatment after surgery, Harmeling et al. by reviewing fourteen studies of 5.270 patients found that mean time from

mastectomy with immediate breast reconstruction to adjuvant therapy varied between 29 and 61 days [100]. Albright et al. retrospectively analysed 129.951 cases comparing NSM to SSM and reported that NSM was not associated with a delay in delivery of adjuvant chemotherapy or hormonal therapy compared to SSM [101]. In the present study, the adjuvant treatment was initiated within 12 weeks after surgery (ASM:7.4 weeks (range: 4.6 – 11.9); NSM: 8.1 weeks (range: 4.1 – 12.0)) in all of the cases in both groups.

Weber et al. reported the recommendations of the Oncoplastic Breast Consortium consensus conference on NSM, which currently provides the highest level of evidence of NSM application [13]. The expert panel of 44 breast surgeons from 14 countries on four continents agreed that NSM is comparable to conventional mastectomy without reconstruction and to BCS and SSM if cases are selected appropriately. Regarding their recommendation for indications, NSM can be performed for any tumour size without skin or NAC involvement independent of axillary status and for DCIS; NSM is also applicable in risk-reducing settings. There was a strong consensus that nipple involvement and R1 resection at the nipple margin are contraindications for nipple preservation. However, the panel was divided in regard to the question of nipple excision with areola preservation if the retroareolar margins were positive. They also noted a 0.81% (n=7) nipple recurrence rate after NSM in a follow-up period of 32 months. The consensus conference concluded that further randomized trials and longer follow-up periods are needed to provide missing evidence and to clarify indications to guide treatment.

The indications for both ASM and NSM in this study were primarily based on theoretical considerations strictly according to the actual international guidelines, not purely on the nipple-tumour distance [13, 41]. Therefore, ASM operations were performed first in this study and replaced by NSM when it was internationally accepted for both prophylactic and therapeutic indications [41]. This resulted in two homogenous study groups, enabling the comparison of the two surgical techniques.

5.5. Assessing the opinions and needs of the Hungarian breast cancer population about a modern breast reconstruction system - based on the results of study 4.3.

The spread of the modern oncoplastic approach has resulted in a paradigm shift in breast cancer treatment [102-104]. Surgical treatment has shifted from breast tumour excision to a complex surgical process including complete breast reconstruction, even bilateral or a series of

operations. This poses a number of system-level tasks, such as the need for lifelong plastic surgical follow-up of reconstructed breasts and the necessary cosmetic corrections in parallel with oncological controls. These needs and indications are new in breast cancer care, the precise definition of which, the clarification of the scope of care and the requirements of material and human resources are essential for the development and high-level long-term operation of a modern patient-centred care system. The basis of all is formed by the recognition and analysation of the needs and expectations of patients.

The present study assessed the systemic needs and expectations of female patients who underwent breast loss and breast reconstruction. It is clear from the results that breast loss significantly disturbs female patients regardless of education and marital status (Figure 5). These findings correspond to the results of a questionnaire survey of 500 female patients between 2010 and 2011 published by our working group in 2014 [103]. According to the study, 30% (n = 148) of patients were moderately and 40% (n = 198) were very afraid of breast loss, nearly 50% (46%; n = 224) wanted reconstruction, but they knew almost nothing (32%; n = 158) or very little (56%; n = 279) about it [103]. Based on oncoplastic breast surgery at the NIO, according to a repetition of the same questionnaire survey conducted in 2017-2018, women are still equally afraid of breast loss, but in contrast to the previous data (10%; n = 48), 30% of the respondents (n = 152) were already aware of the possibilities of breast reconstruction, which information was collected mainly from the surgeon (52%; n = 258) or the internet (27%; n = 135). Based on these, it can be generally stated that breast loss places a significant psychological burden on breast cancer patients regardless of social status and education, therefore, the extension of the oncoplastic care system is needed and necessary in Hungary. In the last 6-8 years, the oncoplastic approach has become widespread and well-known among Hungarian women. In parallel, the population's demand for this special health service is also growing, which the health care system must be able to provide.

Patients have high expectations for the aesthetic outcome of the operations, in total, almost half of the women (48%; n = 239) want more beautiful (28%; n = 140) or perfect (20%; n = 99) breasts at the end of the reconstruction process. Preoperative patient information on realistic expectations is one of the top priorities, because oncoplastic procedures are not aesthetic operations, and albeit they are often capable of the same high level of results as aesthetic surgeries due to their technique, but are completely subordinated to oncological

procedures and principles (e.g. resection site, extent, RT, etc.), thus, their effectiveness is influenced by a number of other factors beyond plastic surgery [105].

The majority of the surveyed female patients (70%; n = 348) would like to have roughly identical breasts naked at the end of the reconstruction surgery, regardless of marital status or education. Given that the structure of the two breasts differs during the most frequently applied implant-based post-mastectomy reconstructions, breast asymmetry will increase over time, since the lifted own healthy breast will behave differently due to its biological properties than an implant-only breast. Based on this, patients have secondary surgical demands due to changes in symmetry over time.

According to the surveyed women, the desired high cosmetic result would like to be achieved by two, but not more, than three or four operations, which, in their view, should be covered by the NEAK. On the one hand, it is necessary to avoid oncology-funded aesthetic surgeries in the future, which also raises ethical and professional issues that are difficult to resolve, on the other hand, treatment consisting of a series of operations is a huge load on the care system - as if the number of surgeries for annual breast cancer had increased by hundreds or thousands of cases. At present, the system is able to provide this in elements, but it is questionable whether it would be able to ensure in total. Therefore, the joint work of patients, profession and professional policy is essential and needed.

Patients would entrust their surgical treatment in specialized centres to specially trained breast surgeons, because, in their opinion, this would have a significant impact on their recovery. In the treatment of breast cancer, the breast surgeon is also an independent prognostic factor [106], but the spread and quality assurance of BUs in Hungary and with BRESO accreditation, the survival as well as the QoL of patients can be further improved in the 21st century [47].

The need for oncoplastic breast reconstruction following mastectomy in Hungary is in line with international trends: according to a British study, 50% of female patients awaiting breast removal [107], while according to a French study by Ananian et al., 81% of respondents would like to have reconstruction [108]. Similar to the international situation, according to our survey, the main source of information for Hungarian patients is also the surgeon and the internet [109, 110]. Understanding the needs of the affected women, providing adequate

information, increasing accessibility, organizing patient routes and properly structuring the health care system are essential for a high level of expansion of oncoplastic breast cancer care [111, 112].

6. CONCLUSIONS

6.1. Our findings suggest that there is no significant correlation between the histopathological parameters of the primary breast tumour and the subregional localisation of the SLN.

The majority of SLNs are located in the anterior and central subregions.

6.2. When primary RT is used to treat the axilla, the contouring of the axillary lymph node levels is necessary for the proper design of the tangential field borders. Our analysis leads to the conclusion that STgF did not provide complete coverage of level I-II axillary lymph nodes.

Tangential field WBI provides limited coverage of the axilla. The use of HTgFs is one means of improving axillary coverage with WBI. Only 65.6% of our patients had complete Level I coverage with HTgFs. In line with previous studies, additional axillary and supraclavicular RT field should be considered to treat the axilla properly.

6.3 Applying the ARM technique and leaving lymph nodes behind in the apical, lateral or posterior axillary subregions may leave behind up to 7.2% of metastatic lymph nodes, which may elevate the risk of possible understaging or undertreatment.

In these cases, clipping the preserved lymph nodes should be mandatory for adjuvant axillary RT.

6.4. Based on our previously discussed results, there is no significant difference in oncological safety, complications, aesthetic results or patient satisfaction between ASM and NSM. Preservation of the nipple doesn’t make oncological difference, while preserving breast projection and natural pigmented skin envelope of the areola seems to have the same importance than the complex NAC itself, resulting in the same cosmetic outcome and patient satisfaction like NSM's.

Moreover, preferring ASM over SSM means that the breast projection remains unchanged, and there is the possibility of nipple reconstruction from the expanded pigmented skin of the areola, resulting in a more natural-appearing NAC. Therefore, ASM could be a suitable treatment option, if NSM is not oncologically feasible. Further prospective randomized studies and long-term follow-ups are needed to support our findings.

6.5. The modern oncoplastic care raises new, complex, systemic professional questions and issues in oncology and reconstructive surgery, which result in new challenges and tasks of patient information, human resource training, care system capacity assessment and funding.

Breast cancer patients want state-of-the-art surgeries performed by qualified breast surgeons in professional centres from which they can expect with confidence their physical and mental recovery.

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8. REFERENCES

1. Kasler, M., Otto, S.,Kenessey, I., [The current situation of cancer morbidity and mortality in the light of the National Cancer Registry]. *Orvosi Hetilap*, 2017. 158(3): p. 84-89.

2. Halsted, W. S., I. The Results of Operations for the Cure of Cancer of the Breast Performed at the Johns Hopkins Hospital from June, 1889, to January, 1894. *Annals of Surgery*, 1894. 20(5): p. 497-555.

3. Houssami, N.,Sainsbury, R., Breast cancer: multidisciplinary care and clinical outcomes. *European Journal of Cancer*, 2006. 42(15): p. 2480-91.

4. Hulvat, M. C., Hansen, N. M.,Jeruss, J. S., Multidisciplinary care for patients with breast cancer. *The Surgical Clinics of North America*, 2009. 89(1): p. 133-76, ix.

5. Goldhirsch, A., Ingle, J. N., Gelber, R. D., et al., Thresholds for therapies: highlights of the St Gallen International Expert Consensus on the primary therapy of early breast cancer 2009. *Annals of Oncology*, 2009. 20(8): p. 1319-29.

6. Goldhirsch, A., Wood, W. C., Coates, A. S., et al., Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Annals of Oncology*, 2011. 22(8): p. 1736-47.

7. Kasler, M., Polgar, C.,Fodor, J., [Current status of treatment for early-stage invasive breast cancer]. *Orvosi Hetilap*, 2009. 150(22): p. 1013-21.

8. Curigliano, G., Burstein, H. J., Winer, E. P., et al., De-escalating and escalating treatments for early-stage breast cancer: the St. Gallen International Expert Consensus Conference on the Primary Therapy of Early Breast Cancer 2017. *Annals of Oncology*, 2017. 28(8): p. 1700-1712.

9. Pilewskie, M.,Morrow, M., Margins in breast cancer: How much is enough? *Cancer*, 2018. 124(7): p. 1335-1341.

10. Cavalcante, F. P., Millen, E. C., Zerwes, F. P., et al., Role of Axillary Surgery After Neoadjuvant Chemotherapy. *JCO Global Oncology*, 2020. 6: p. 238-241.

11. Henke, G., Knauer, M., Ribi, K., et al., Tailored axillary surgery with or without axillary lymph node dissection followed by radiotherapy in patients with clinically node-

positive breast cancer (TAXIS): study protocol for a multicenter, randomized phase-III trial. *Trials*, 2018. 19(1): p. 667-667.

12. Kanbayashi, C., Thompson, A. M., Hwang, E.-S. S., et al., The international collaboration of active surveillance trials for low-risk DCIS (LORIS, LORD, COMET, LORETTA). *Journal of Clinical Oncology*, 2019. 37(15_suppl): p. TPS603-TPS603.

13. Weber, W. P., Haug, M., Kurzeder, C., et al., Oncoplastic Breast Consortium consensus conference on nipple-sparing mastectomy. *Breast Cancer Research and Treatment*, 2018. 172(3): p. 523-537.

14. Macéa, J. R.,Fregnani, J. H. T. G., Anatomy of the Thoracic Wall, Axilla and Breast. *International Journal of Morphology*, 2006. 24: p. 691-704.

15. Berg, J. W., The significance of axillary node levels in the study of breast carcinoma. *Cancer*, 1955. 8(4): p. 776-8.

16. Ibusuki, M., Yamamoto, Y., Kawasoe, T., et al., Potential advantage of preoperative three-dimensional mapping of sentinel nodes in breast cancer by a hybrid single photon emission CT (SPECT)/CT system. *Surgical Oncology*, 2010. 19(2): p. 88-94.

17. Gallowitsch, H. J., Kraschl, P., Igerc, I., et al., Sentinel node SPECT-CT in breast cancer. Can we expect any additional and clinically relevant information? *Nuklearmedizin. Nuclear medicine*, 2007. 46(6): p. 252-256.

18. Giuliano, A. E., Haigh, P. I., Brennan, M. B., et al., Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. *Journal of Clinical Oncology*, 2000. 18(13): p. 2553-9.

19. Krag, D., Weaver, D., Ashikaga, T., et al., The Sentinel Node in Breast Cancer — A Multicenter Validation Study. *New England Journal of Medicine*, 1998. 339(14): p. 941-946.

20. Peley, G., Sinkovics, I., Liszkay, G., et al., [The role of intraoperative gamma-probe-guided sentinel lymph node biopsy in the treatment of malignant melanoma and breast cancer]. *Orvosi Hetilap*, 1999. 140(42): p. 2331-8.

21. Coates, A. S., Winer, E. P., Goldhirsch, A., et al., Tailoring therapies--improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. *Annals of Oncology*, 2015. 26(8): p. 1533-46.

22. National ComprehensiveCancer Network (NCCN) Clinical Practice Guidelines in Clinical Oncology. Breast Cancer. Version 3.2017. www.nccn.org 11/10/17.

23. Matrai, Z., Toth, L., Saeki, T., et al., [The potential role of SPECT/CT in the preoperative detection of sentinel lymph nodes in breast cancer]. *Orvosi Hetilap*, 2011. 152(17): p. 678-88.

24. Giuliano, A. E., Ballman, K., McCall, L., et al., Locoregional Recurrence After Sentinel Lymph Node Dissection With or Without Axillary Dissection in Patients With Sentinel Lymph Node Metastases: Long-term Follow-up From the American College of Surgeons Oncology Group (Alliance) ACOSOG Z0011 Randomized Trial. *Annals of Surgery*, 2016. 264(3): p. 413-20.

25. Giuliano, A. E., Hunt, K. K., Ballman, K. V., et al., Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *The Journal of the American Medical Association*, 2011. 305(6): p. 569-75.

26. Jagsi, R., Chadha, M., Moni, J., et al., Radiation field design in the ACOSOG Z0011 (Alliance) Trial. *Journal of Clinical Oncology*, 2014. 32(32): p. 3600-6.

27. Beek, M. A., Gobardhan, P. D., Schoenmaeckers, E. J., et al., Axillary reverse mapping in axillary surgery for breast cancer: an update of the current status. *Breast Cancer Research and Treatment*, 2016. 158(3): p. 421-32.

28. Nos, C., Clough, K. B., Bonnier, P., et al., Upper outer boundaries of the axillary dissection. Result of the SENTIBRAS protocol: Multicentric protocol using axillary reverse mapping in breast cancer patients requiring axillary dissection. *European Journal of Surgical Oncology*, 2016. 42(12): p. 1827-1833.

29. Tummel, E., Ochoa, D., Korourian, S., et al., Does Axillary Reverse Mapping Prevent Lymphedema After Lymphadenectomy? *Annals of Surgery*, 2017. 265(5): p. 987-992.

30. Han, C., Yang, B., Zuo, W. S., et al., The Feasibility and Oncological Safety of Axillary Reverse Mapping in Patients with Breast Cancer: A Systematic Review and Meta-Analysis of Prospective Studies. *Public Library of Science*, 2016. 11(2): p. e0150285.

31. Murthy, V.,Chamberlain, R. S., Defining a place for nipple sparing mastectomy in modern breast care: an evidence based review. *The Breast Journal*, 2013. 19(6): p. 571-81.

32. van Verschuer, V. M., van Deurzen, C. H., Westenend, P. J., et al., Prophylactic nipple-sparing mastectomy leaves more terminal duct lobular units in situ as compared with

skin-sparing mastectomy. *The American Journal of Surgical Pathology*, 2014. 38(5): p. 706-12.

33. Kato, M.,Simmons, R. M., Nipple- and Areola-Sparing Mastectomy., in Breast Surgical Oncology, H.M. Kuerer, Editor. 2010, *McGraw-Hill Professional*: United States of America. p. 711-717.

34. Kryvenko, O. N., Yoon, J. Y., Chitale, D. A., et al., Prevalence of terminal duct lobular units and frequency of neoplastic involvement of the nipple in mastectomy. *Archives of Pathology & Laboratory Medicine*, 2013. 137(7): p. 955-60.

35. Russo, J., Hu, Y. F., Yang, X., et al., Developmental, cellular, and molecular basis of human breast cancer. *Journal of the National Cancer Institute. Monographs*, 2000(27): p. 17-37.

36. Schnarr, K., Fan, F., Amin, A. L., et al., Comparison of terminal duct lobular units in the nipple areolar complex by tumor subtypes-the implication for nipple sparing mastectomy. *Journal of Clinical Oncology*, 2017. 35(15_suppl): p. e12082-e12082.

37. Stolier, A. J.,Wang, J., Terminal duct lobular units are scarce in the nipple: implications for prophylactic nipple-sparing mastectomy: terminal duct lobular units in the nipple. *Annals of Surgical Oncology*, 2008. 15(2): p. 438-42.

38. Rusby, J. E., Brachtel, E. F., Michaelson, J. S., et al., Breast duct anatomy in the human nipple: three-dimensional patterns and clinical implications. *Breast Cancer Research and Treatment*, 2007. 106(2): p. 171-9.

39. Rusby, J. E., Brachtel, E. F., Taghian, A., et al., George Peters Award. Microscopic anatomy within the nipple: implications for nipple-sparing mastectomy. *American Journal of Surgery*, 2007. 194(4): p. 433-7.

40. Galimberti, V., Vicini, E., Corso, G., et al., Nipple-sparing and skin-sparing mastectomy: Review of aims, oncological safety and contraindications. *Breast*, 2017. 34 Suppl 1: p. S82-S84.

41. Mallon, P., Feron, J. G., Couturaud, B., et al., The role of nipple-sparing mastectomy in breast cancer: a comprehensive review of the literature. *Plast Reconstr Surg*, 2013. 131(5): p. 969-84.

42. Tousimis, E.,Haslinger, M., Overview of indications for nipple sparing mastectomy. *Gland Surg*, 2018. 7(3): p. 288-300.

43. Goldhirsch, A., Winer, E. P., Coates, A. S., et al., Personalizing the treatment of women with early breast cancer: highlights of the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2013. *Annals of Oncology*, 2013. 24(9): p. 2206-23.

44. Cataliotti, L., Costa, A., Daly, P. A., et al., Florence statement on breast cancer, 1998 forging the way ahead for more research on and better care in breast cancer. *European Journal of Cancer*, 1999. 35(1): p. 14-5.

45. The requirements of a specialist breast unit. *European Journal of Cancer*, 2000. 36(18): p. 2288-93.

46. Piccart, M., Cataliotti, L., Buchanan, M., et al., Brussels Statement document. *European Journal of Cancer*, 2001. 37(11): p. 1335-7.

47. Kovacs, T., Rubio, I. T., Markopoulos, C., et al., Theoretical and practical knowledge curriculum for European Breast Surgeons. *European Journal of Surgical Oncology*, 2020. 46(4 Pt B): p. 717-736.

48. Wilson, A. R., Marotti, L., Bianchi, S., et al., The requirements of a specialist Breast Centre. *European Journal of Cancer*, 2013. 49(17): p. 3579-87.

49. Biganzoli, L., Marotti, L., Hart, C. D., et al., Quality indicators in breast cancer care: An update from the EUSOMA working group. *European Journal of Cancer*, 2017. 86: p. 59-81.

50. Perry, N., Broeders, M., de Wolf, C., et al., European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition--summary document. *Annals of Oncology*, 2008. 19(4): p. 614-22.

51. Ujhelyi, M., Pukancsik, D., Kelemen, P., et al., [Breast cancer care quality analysis of the National Institute of Oncology in Hungary according to the requirements of European Society of Breast Cancer Specialists (EUSOMA)]. *Orvosi Hetilap*, 2016. 157(42): p. 1674-1682.

52. Andree, C., Farhadi, J., Goossens, D., et al., A position statement on optimizing the role of oncoplastic breast surgery. *Eplasty*, 2012. 12: p. e40.

53. Emiroglu, M., Sert, I.,Inal, A., The Role of Oncoplastic Breast Surgery in Breast Cancer Treatment. *The Journal of Breast Health*, 2015. 11(1): p. 1-9.

54. Macmillan, R. D.,McCulley, S. J., Oncoplastic Breast Surgery: What, When and for Whom? *Current Breast Cancer Reports*, 2016. 8: p. 112-117.

55. Harnett, A., Smallwood, J., Titshall, V., et al., Diagnosis and treatment of early breast cancer, including locally advanced disease--summary of NICE guidance. *British Medical Journal*, 2009. 338: p. b438.

56. Makari-Judson, G., Braun, B., Jerry, D. J., et al., Weight gain following breast cancer diagnosis: Implication and proposed mechanisms. *World Journal of Clinical Oncology*, 2014. 5(3): p. 272-82.

57. Nyrop, K. A., Williams, G. R., Muss, H. B., et al., Weight gain during adjuvant endocrine treatment for early-stage breast cancer: What is the evidence? *Breast Cancer Research and Treatment*, 2016. 158(2): p. 203-17.

58. Raghavendra, A., Sinha, A. K., Valle-Goffin, J., et al., Determinants of Weight Gain During Adjuvant Endocrine Therapy and Association of Such Weight Gain With Recurrence in Long-term Breast Cancer Survivors. *Clinical Breast Cancer*, 2018. 18(1): p. e7-e13.

59. Machida, Y.,Nakadate, M., Breast Shape Change Associated with Aging: A Study Using Prone Breast Magnetic Resonance Imaging. *Plastic and Reconstructive Surgery. Global Open*, 2015. 3(6): p. e413-e413.

60. Nie, K., Su, M. Y., Chau, M. K., et al., Age- and race-dependence of the fibroglandular breast density analyzed on 3D MRI. *Medical Physics*, 2010. 37(6): p. 2770-6.

61. Wolfe, J. N., Breast parenchymal patterns and their changes with age. *Radiology*, 1976. 121(3 Pt. 1): p. 545-52.

62. Momoh, A. O., Ahmed, R., Kelley, B. P., et al., A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy. *Annals of Surgical Oncology*, 2014. 21(1): p. 118-24.

63. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Clinical Oncology. Breast Cancer. Version 1.2013, www.nccn.org 02/01/13.

64. Senkus, E., Kyriakides, S., Penault-Llorca, F., et al., Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 2013. 24 Suppl 6: p. vi7-23.

65. Kasler, M., [Recommendations of the 2nd Breast Cancer Consensus Conference (Kecskemet, November 8-9, 2009) -- Introduction]. *Magyar Onkológia*, 2010. 54(3): p. 209.

66. Cserni, G., Francz, M., Járay, B., et al., Az emlőrák patológiai diagnosztikája, feldolgozása és kórszövettani leletezése. *Magyar Onkológia*, 2010. 54: p. 217-226.

67. Lester, S. C., Bose, S., Chen, Y. Y., et al., Protocol for the examination of specimens from patients with invasive carcinoma of the breast. *Archives of Pathology & Laboratory Medicine*, 2009. 133(10): p. 1515-38.

68. White, J., Tai, A., Arthur, D., et al., Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definition. RTOG website: www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.

69. Hammer, Ø., Harper, D. A. T.,Ryan, P. D., PAST: Paleontological Statistics software package for education and data analysis. *Palaeontologia Electronica*, 2001. 4: p. 1-9.

70. Offersen, B. V., Boersma, L. J., Kirkove, C., et al., ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. *Radiotherapy and Oncology*, 2015. 114(1): p. 3-10.

71. Senkus, E., Kyriakides, S., Ohno, S., et al., Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*, 2015. 26 Suppl 5: p. v8-30.

72. Kronowitz, S. J., Hunt, K. K., Kuerer, H. M., et al., Delayed-immediate breast reconstruction. *Plastic and Reconstructive Surgery*, 2004. 113(6): p. 1617-28.

73. Clavien, P. A., Barkun, J., de Oliveira, M. L., et al., The Clavien-Dindo classification of surgical complications: five-year experience. *Annals of Surgery*, 2009. 250(2): p. 187-96.

74. Dindo, D., Demartines, N.,Clavien, P. A., Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Annals of Surgery*, 2004. 240(2): p. 205-13.

75. Dikmans, R. E. G., Nene, L. E. H., Bouman, M. B., et al., The Aesthetic Items Scale: A Tool for the Evaluation of Aesthetic Outcome after Breast Reconstruction. *Plastic and Reconstructive Surgery. Global Open*
2017. 5(3): p. e1254.

76. Pusic, A. L., Klassen, A. F., Scott, A. M., et al., Development of a new patient-reported outcome measure for breast surgery: the BREAST-Q. *Plastic and Reconstructive Surgery*, 2009. 124(2): p. 345-53.

77. Nyerges, G., [Ethical implications of scientific human experiments]. *Orvosi Hetilap*, 1985. 126(24): p. 1451-8.

78. Gradishar, W. J., Anderson, B. O., Balassanian, R., et al., Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. *Journal of the National Comprehensive Cancer Network* 2016. 14(3): p. 324-54.

79. Lazar, G., Bursics, A., Farsang, Z., et al., [Modern surgical treatment of breast cancer. 3rd Breast Cancer Consensus Conference]. *Magyar Sebészet*, 2016. 69(3): p. 117-32.

80. Reed, D. R., Lindsley, S. K., Mann, G. N., et al., Axillary lymph node dose with tangential breast irradiation. *International Journal of Radiation Oncology, Biology, Physics*, 2005. 61(2): p. 358-64.

81. Krasin, M., McCall, A., King, S., et al., Evaluation of a standard breast tangent technique: a dose-volume analysis of tangential irradiation using three-dimensional tools. *International Journal of Radiation Oncology, Biology, Physics*, 2000. 47(2): p. 327-33.

82. Reznik, J., Cicchetti, M. G., Degaspe, B., et al., Analysis of axillary coverage during tangential radiation therapy to the breast. *International Journal of Radiation Oncology, Biology, Physics*, 2005. 61(1): p. 163-8.

83. Orecchia, R., Huscher, A., Leonardi, M. C., et al., Irradiation with standard tangential breast fields in patients treated with conservative surgery and sentinel node biopsy: Using a three-dimensional tool to evaluate the first level coverage of the axillary nodes. *The British Journal of Radiology*, 2005. 78: p. 51-4.

84. Ohashi, T., Takeda, A., Shigematsu, N., et al., Dose distribution analysis of axillary lymph nodes for three-dimensional conformal radiotherapy with a field-in-field technique for breast cancer. *International Journal of Radiation Oncology, Biology, Physics*, 2009. 73(1): p. 80-7.

85. Nagar, H., Zhou, L., Biritz, B., et al., Is There a Tradeoff in Using Modified High Tangent Field Radiation for Treating an Undissected Node-Positive Axilla? *Clinical Breast Cancer*, 2014. 14(2): p. 109-113.

86. Belkacemi, Y., Allab-Pan, Q., Bigorie, V., et al., The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I-II and the sentinel node area. *Annals of Oncology*, 2013. 24(8): p. 2023-8.

87. Alco, G., Igdem, S. I., Ercan, T., et al., Coverage of axillary lymph nodes with high tangential fields in breast radiotherapy. *The British Journal of Radiology*, 2010. 83(996): p. 1072-6.

88. Savolt, A., Peley, G., Polgar, C., et al., Eight-year follow up result of the OTOASOR trial: The Optimal Treatment Of the Axilla - Surgery Or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: A randomized, single centre, phase III, non-inferiority trial. *European Journal of Surgical Oncology*, 2017. 43(4): p. 672-679.

89. Ikeda, K., Ogawa, Y., Komatsu, H., et al., Evaluation of the metastatic status of lymph nodes identified using axillary reverse mapping in breast cancer patients. *World Journal of Surgical Oncology*, 2012. 10: p. 233-233.

90. Bedrosian, I., Babiera, G. V., Mittendorf, E. A., et al., A phase I study to assess the feasibility and oncologic safety of axillary reverse mapping in breast cancer patients. *Cancer*, 2010. 116(11): p. 2543-8.

91. Schunemann, E., Jr., Doria, M. T., Silvestre, J. B., et al., Prospective study evaluating oncological safety of axillary reverse mapping. *Annals of Surgical Oncology*, 2014. 21(7): p. 2197-202.

92. Rubio , I. T., Luiten, E. J. T.,Klimberg, V. S., Axillary Reverse Mapping: ARM in Breast Cancer Management for Surgeons, L. Wyld, et al., Editors. 2018, *Springer International Publishing*: Switzerland. p. 303-312.

93. Headon, H. L., Kasem, A.,Mokbel, K., The Oncological Safety of Nipple-Sparing Mastectomy: A Systematic Review of the Literature with a Pooled Analysis of 12,358 Procedures. *Archives of Plastic Surgery*, 2016. 43(4): p. 328-38.

94. Didier, F., Radice, D., Gandini, S., et al., Does nipple preservation in mastectomy improve satisfaction with cosmetic results, psychological adjustment, body image and sexuality? *Breast Cancer Research and Treatment*, 2009. 118(3): p. 623-33.

95. Cunnick, G. H.,Mokbel, K., Oncological considerations of skin-sparing mastectomy. *International Seminars in Surgical Oncology*, 2006. 3: p. 14.

96. Simmons, R. M., Brennan, M., Christos, P., et al., Analysis of nipple/areolar involvement with mastectomy: can the areola be preserved? *Annals of Surgical Oncology*, 2002. 9(2): p. 165-8.

97. Banerjee, A., Gupta, S.,Bhattacharya, N., Preservation of nipple-areola complex in breast cancer--a clinicopathological assessment. *Journal of Plastic, Reconstructive & Aesthetic Surgery*, 2008. 61(10): p. 1195-8.

98. Simmons, R. M., Hollenbeck, S. T.,Latrenta, G. S., Areola-sparing mastectomy with immediate breast reconstruction. *Annals of Plastic Surgery*, 2003. 51(6): p. 547-51.

99. Simmons, R. M., Hollenbeck, S. T.,Latrenta, G. S., Two-year follow-up of areola-sparing mastectomy with immediate reconstruction. *American Journal of Surgery*, 2004. 188(4): p. 403-6.

100. Harmeling, X. J., Kouwenberg, C. A., Bijlard, E., et al., The effect of immediate breast reconstruction on the timing of adjuvant chemotherapy: a systematic review. *Breast Cancer Research and Treatment*, 2015. 153(2): p. 241-51.

101. Albright, E. L., Schroeder, M. C., Foster, K., et al., Nipple-Sparing Mastectomy is Not Associated with a Delay of Adjuvant Treatment. *Annals of Surgical Oncology*, 2018. 25(7): p. 1928-1935.

102. Matrai, Z., Gulyas, G., Toth, L., et al., [Challenges in oncologic plastic surgery of the breast]. *Magyar Onkológia*, 2011. 55(1): p. 40-52.

103. Matrai, Z., Kenessey, I., Savolt, A., et al., Evaluation of patient knowledge, desire, and psychosocial background regarding postmastectomy breast reconstruction in Hungary: a questionnaire study of 500 cases. *Medical Science Monitor*, 2014. 20: p. 2633-42.

104. Pukancsik, D., Kelemen, P., Savolt, A., et al., [Evaluation of clinicopathological findings and cosmetic outcome of 100 immediate postmastectomy breast reconstruction cases]. *Orvosi Hetilap*, 2016. 157(46): p. 1830-1838.

105. Pukancsik, D., Kelemen, P., Ujhelyi, M., et al., Objective decision making between conventional and oncoplastic breast-conserving surgery or mastectomy: An aesthetic and functional prospective cohort study. *European Journal of Surgical Oncology*, 2017. 43(2): p. 303-310.

106. Cataliotti, L., De Wolf, C., Holland, R., et al., Guidelines on the standards for the training of specialised health professionals dealing with breast cancer. *European Journal of Cancer*, 2007. 43(4): p. 660-75.

107. Keith, D. J., Walker, M. B., Walker, L. G., et al., Women who wish breast reconstruction: characteristics, fears, and hopes. *Plastic and Reconstructive Surgery*, 2003. 111(3): p. 1051-6; discussion 1057-9.

108. Ananian, P., Houvenaeghel, G., Protiere, C., et al., Determinants of patients' choice of reconstruction with mastectomy for primary breast cancer. *Annals of Surgical Oncology*, 2004. 11(8): p. 762-71.

109. Alderman, A. K., Hawley, S. T., Waljee, J., et al., Understanding the impact of breast reconstruction on the surgical decision-making process for breast cancer. *Cancer*, 2008. 112(3): p. 489-94.

110. Morrow, M., Mujahid, M., Lantz, P. M., et al., Correlates of breast reconstruction: results from a population-based study. *Cancer*, 2005. 104(11): p. 2340-6.

111. Flitcroft, K., Brennan, M.,Spillane, A., Making decisions about breast reconstruction: A systematic review of patient-reported factors influencing choice. *Quality of Life Research*, 2017. 26(9): p. 2287-2319.

112. Retrouvey, H., Zhong, T., Gagliardi, A. R., et al., How patient acceptability affects access to breast reconstruction: a qualitative study. *British Medical Journal Open*, 2019. 9(9): p. e029048.

9. APPENDIX

I.

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Mapping of the functional anatomy of lymphatic drainage to the axilla in early breast cancer: A cohort study of 933 cases

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Abbreviations:
ARM
Axillary reverse mapping
ALND
Axillary lymph node dissection
BCS
Breast-conserving surgery
HTgF
High tangential fieldRT
Radiotherapy
SLN
Sentinel lymph node
SLNB

ABSTRACT

Introduction: The aims of this study were to investigate the correlation between lymphatic drainage and the sentinel lymph node (SLN) status of the subregions in the context of the clinic-pathological parameters of the tumour and the coverage of the axillary volumes by standard and high tangential fields (STgF and HTgF) for whole breast radiotherapy and axillary reverse mapping (ARM).
Patients and methods: 933 women with early breast cancer and clinically negative axillary status underwent breast surgery and SLN biopsy followed by axillary lymph node dissection in SLN-positive cases. The subregional localisation of the SLN(s) was registered and statistically analysed with the clinic-pathological characteristics of the breast tumour. In node-positive patients treated with breast-conserving therapy in whom the SLNs were found in the anterior or posterior axillary subregions, the axillary volumes were contoured using the Radiation Therapy Oncology Group contouring atlas (n = 61).
Results: In 91.1% (n = 797) of the cases, the SLN appeared in the anterior, posterior or central subregions. Using HTgF, Level I or II were completely covered in 65.6% (40/61) and 6.6% (4/61) of the cases, respectively. With STgF, the complete coverage was 0% for both levels.
6.8% (n = 63) of all cases had one positive lymph node in the expected ARM lymph node regions.
Discussion: A SLN is more than likely to be present in the anterior, posterior and central axillary subregions. Tangential fields allow only limited coverage of the axillary volumes. Preserving the lateral subregion during ARM may increase the possibility of understaging.

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Sentinel lymph node biopsy
STgF
Standard tangential field
WBI
Whole breast irradiation
na
Not applicable

Introduction

Regional lymph node status is one of the most important prognostic factors for disease-free and overall survival in breast cancer [1–5]. Today, the gold-standard method for staging patients with early-stage breast cancer with clinically negative axillary lymph nodes is the sentinel lymph node biopsy (SLNB) [4,5].

To optimise the effectiveness of SLNB, the precise pre- and intraoperative mapping of lymphatic drainage is mandatory [4–6].

Anatomically, the axillary region is divided into five subregions: anterior, posterior, lateral, central and apical zones [7] (Fig. 1).

The anterior subregion is located under the lateral edge of the pectoralis minor muscle along the lateral thoracic vein. The posterior zone is found adjacent to the posterior wall of the axilla along the thoracodorsal nerve and vessels. The lateral subregion is located close to the lateral wall of the axilla, in relation to the proximal part of the axillary vein. The lymph nodes in this zone receive the vast majority of the efferent lymph vessels of the upper limb. The central zone is in the middle of the pyramid-shaped space of the armpit, close to the base of the axilla. The apical subregion is found in the apex medially to the distal part of the axillary vein.

These subregions correspond to the axillary node levels previously described by Berg [8]. The anterior, posterior and lateral subregions constitute Level I, the central zone forms Level II and the apical zone constitutes Level III [7].

Clear relationships between the anatomic location and metastatic status of the SLN have been revealed [9,10]. Histologically positive SLN was detected in Level I in 96% of cases and in Level II in 4% of cases by SPECT/CT [10].

A better understanding of the relationships between the subregional drainage pattern of SLN, the subregional localisation of SLN and the correlation to location and pathological characteristics of the primary breast tumour could have particular importance in determining whether ALND can be safely omitted.

The ACOSOG Z0011 trial did not perform ALND for early-stage breast cancer patients with 1–2 metastatic SLNs (cT1-2, pN1), and in the majority of the patients, the axilla was treated only with tangential field irradiation following breast-conserving surgery (BCS). After a median follow-up of 9.3 years, the data compared to the traditional ALND group showed no differences in local recurrence-free survival [11,12]. However, in the ACOSOG Z0011 trial, dose distribution in the axillary volumes was not reported in the initial publication. Jagsi et al. [13] recently analysed the radiotherapy (RT) coverage of the axillary lymph nodes of that trial. Most patients treated in the Z0011 trial received tangential RT alone, and some received no RT at all. Some patients received directed nodal irradiation via a third field. They concluded that further research is necessary to determine the optimal RT approach in patients with low-volume axillary disease treated with SLNB alone.

A recent surgical technique that is less radical and therefore decreases the morbidity of SLNB and ALND, especially lymphedema, is ARM [14–16]. The lymphatic drainage of the upper limb that runs through the axilla - most often the lateral subregional lymphatic structures - is identified by injecting radioisotope or blue dye to the ipsilateral limb subcutaneously, and these nodes are spared during the operation, removing only the lymph nodes that drain the lymph of the breast. The technique was proven to be feasible with a low level of evidence; however, the question of oncological radicality still arises due to the uncertainty of the metastatic status of the ARM lymph nodes that are not removed [17].

We sought to determine whether there is a correlation between the lymphatic drainage and the SLN status of the subregions. Our main objectives were as follows:

- To examine the location of the SLN in the axillary subregions in a representative cohort of patients with early-stage breast cancer.
- To assess statistical correlations between the clinicopathological characteristics of the primary breast tumour and the subregion of the SLN.
- To analyse the subregional localisation of metastatic SLNs.
- To assess the statistical correlation between axillary subregions outside the tangential and extended tangential RT coverage field applied in the ACOSOG Z0011 trial and the SLN positivity within these subregions after BCS.
- To study the axillary coverage with STgF or HTgF irradiation in node-positive patients.
- To assess the SLN positivity rate in the lateral, unremoved subregion when the ARM technique is applied.

Patients and methods

A retrospective cohort study was performed between March 2013 and February 2015. 933 female patients older than 18 years were enrolled with primary unilateral invasive or microinvasive, clinically lymph node-negative early-stage breast cancer (clinically $T \leq 5$ cm, N0M0). Exclusion criteria included previous ALND, cN1-2, pregnancy, lactation and necessity of neoadjuvant treatment for breast cancer [18,19].

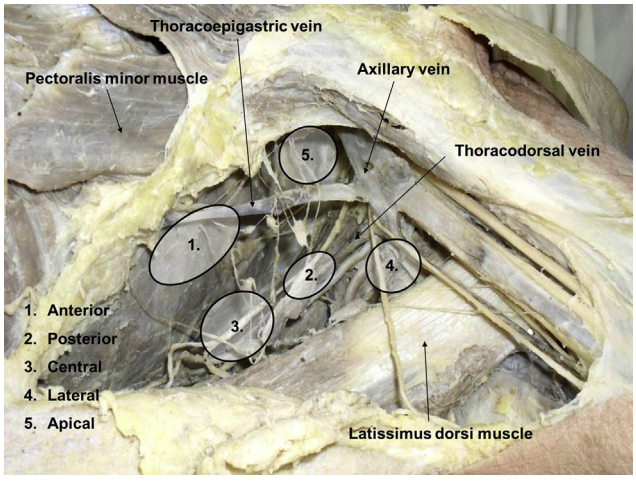

Fig. 1. Subregions of the axilla (left side, human cadaveric dissection).

The complex oncological therapy was performed according to the actual international guidelines [18–20] adopted by the National Institute of Oncology and was not different from those who were not included in the trial. Radiopharmaceutical (80 Mbq ^{99m} Tc labelled nanocolloid, particle size: 50–800 nm) was injected to the intratumoural area or periareolar tissue on the day before surgery. If the lymphoscintigraphy was unsuccessful, 2–3 ml of periareolar Patent blue 25 mg/ml® dye injection was applied 10 min before the operation.

Patients then underwent a wide excision or mastectomy and axillary SLNB followed by ALND instantly if the SLN was positive by intraoperative imprint cytology or as a second operation if the SLN was positive only by histological examination. If isolated tumour cells or micrometastases were found in the SLN (n = 33), ALND was omitted.

The subregional localisation of the SLN(s) was identified and recorded on a standardised data sheet by the operating surgeons immediately after biopsy in the operating theatre (Fig. 1). The harvested SLNs were separated and labelled with their localisation for pathological processing. Imprint cytology was performed intraoperatively, and if the result was positive, the operation was completed with ALND. Postoperatively, all the removed lymph nodes were meticulously examined by the pathologists according to the guidelines [21,22]. In cases of false negative SLNB, the subregional localisation and the number of metastatic lymph nodes left behind in the axilla could not be identified by our applied methods.

Following BCS, all patients had 3D-conformal RT. Patients were placed supine with both arms up and both hands holding on to a support during CT simulation. CT scan images with 5-mm sections were obtained. The breast was irradiated with two opposing tangential fields with 6 MV photons. STgF margins were determined by palpation of the breast parenchyma with the addition of a 1–2-cm margin in all directions. The superior borders of these fields intended to treat the breast only, without regard to nodal coverage. Approximately 2 cm (max. 3 cm) of the lung was included in the posterior aspect of the field. In node-positive patients, an additional field was also used to deliver an effective dose to the axillary apex and clavicular fossa. The total dose of the whole breast and supraclavicular fossa was 50 Gy (25 × 2 Gy). Breast irradiation was given via STgFs. The STgF upper margin was generally the base (±1 cm) of the clavicle. Retrospectively, for the purpose of this study in 61 randomly selected node-positive patients treated with breast-conserving therapy in whom the SLNs were found in the anterior or posterior axillary subregions (Level I), HTgFs were simulated using the same CT data. HTgF consisted of a superior border placed at the inferior edge (or below maximum 2 cm) of the humeral head. Before RT planning, axillary volumes (Levels I, II and III) were contoured using the RTOG (Radiation Therapy Oncology Group) contouring atlas [23]. Coverage of the axillary volumes by tangential fields was classified according to the tangential field-planning target volumes (Levels I, II and III) overlap: 100% overlap (complete coverage), <100% overlap (partial coverage), and 0% overlap (lack of coverage: out of field). Examples of coverages are given in Fig. 2.

The study was approved by the institutional ethical committee board and was registered on Clinicaltrials.gov (identifier: NCT01804309).

The clinical trial did not alter the lege artis oncological treatment and SLN intervention in any way.

All the collected data were registered in the institutional database and statistically analysed using Fisher's exact test. P-values less than 0.05 were considered statistically significant. Statistical analysis was performed using Statistica 12.0 software (StatSoft, Tulsa, OK) or PAST version 1.86b [24].

Results

A total of 933 women were enrolled in the study. The mean age of the patients was 64.1 years (range 19–91 years, median: 64 years). Three women were excluded because the breast tumour was larger than 5 cm according to the postoperative pathologic examination. Another two patients were ruled out due to newly discovered lympho-proliferative disorders affecting the axillary lymph nodes. Another 58 patients were discarded because of an uninterpretable sentinel data sheet or incomplete clinical-histological data.

The detailed pathologic characteristics of the primary breast tumours are summarised in Table 1.

Regarding the location of the breast cancer, 44.7% (n = 417) were in the upper-outer, 14.7% (n = 137) in the upper-inner, 9.9% (n = 93) in the lower-outer, 6.7% (n = 63) in the lower-inner quadrant, and 2.8% (n = 27) in the axillary process (tail of Spence); 12.8% (n = 119) were central tumours and 3.5% (n = 33) were multiplex.

There was a significant correlation between the location and the molecular subtype of the tumour (p = 0.022). Non-luminal tumours were mainly localised in the upper quadrants (84.6% n = 11).

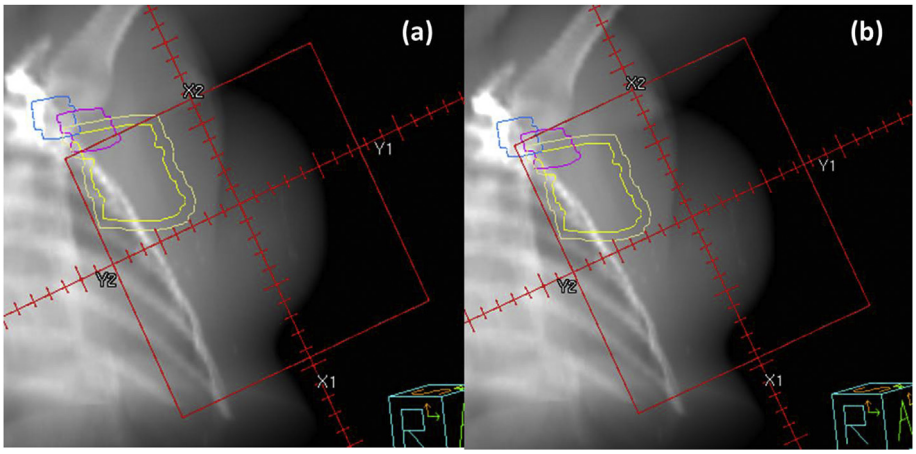

Fig. 2. (a) Coverage with standard tangential field (red square). Yellow lines = Level I volumes: inner line - clinical target volume; outer line - planning target volume; partial coverage. Purple line = Level II clinical target volume; partial coverage. Blue line = Level III clinical target volume; no coverage, out of field. (b) Coverage with high tangential field (red square). Yellow lines = Level I volumes: inner line - clinical target volume; outer line - planning target volume; complete coverage. Purple line = Level II clinical target volume; partial coverage. Blue line = Level III clinical target volume; partial coverage.

Similarly, the triple negative subtype was also likely to appear in the upper-outer quadrant (57.1%; n = 40). However, cancers in the lower-inner quadrant were mostly Her2-enriched (17.1%; n = 7). [Table 2.].

The tracer for lympho-scintigraphy was injected intratumorally and periareolarly in 38.8% (n = 362) and 57.6% (n = 537) of the cases, respectively. We used only radiopharmaceutical (80 Mbq ^{99m}Tc labelled nanocolloid) in 86.9% (n = 811), Patent blue dye in 4.4% (n = 41) and both in 4.8% (n = 45) of the cases.

None of the examined characteristics of the primary breast cancer (molecular subtype p = 0.360) had significant correlation with the subregional localisation of the SLN.

We divided our study population into two groups based on the injection site and analysed the relationships between the location of the SLN and location of the primary breast tumour. In case of intratumoural application, we found significant correlation between the location of the breast cancer and the subregional location of the SLN (p = 0.016). However, examining only the histologically positive SLNs, the relationship between their location and the primary tumour location was not statistically significant (p = 0.674).

If periareolar injections were used, the location of the SLN was not dependent on the location of the primary breast tumour (p = 0.398), whilst the correlation between the location of the positive SLN and the location of the breast cancer was statistically significant (p = 0.039). [Table 3.].

According to our data, tumours in the upper-outer quadrant are least frequently drained to the anterior subregion (34.2%). Posterior subregion receives lymph mainly from the upper-outer quadrant (31.6%) and the axillary process (36.3%), whereas the inner and central quadrants have very similar drainage patterns with a tendency to give efferent lymphatics more often to the anterior (53.9%, 69.6% and 54.5%) and central (28.8%, 26.1% and 22.7%) lymph nodes. The central lymph nodes receive lymphatic drainage equally from the different quadrants of the breast [Table 3.].

An average of 1.6 (range: 1–8, median: 1) SLNs were harvested per operation, and the SLN positivity rate was 20.3% (n = 189).

We also analysed the distribution pattern and metastatic status of the SLN in the subregions of the axilla [Table 3.]. The most common site of the SLN was the anterior subregion (39.9%; n = 349), while the least common was the apical subregion (3.4%; n = 30). In contrast, the positivity rate was higher in the apical subregion (30.0%; n = 9) than in the anterior subregion (20.9%; n = 73). The SLN was present in the lateral subregion in 5.5% (n = 48) of the cases. Of these 48 lymph nodes, 11 SLNs - 1.3% of the total cases - were positive. In the central and posterior subregions, 53 (6.1%) and 43 (4.9%) SLNs, respectively, were found to be positive out of the 245 (28.0%) and 203 (23.2%) removed lymph nodes, respectively.

In 91.1% (n = 797) of the cases, the SLN appeared in the anterior, posterior or central subregions, corresponding to Level I and II zones [Table 3].

In 503 patients, the SLN was located within the anterior or posterior subregion (Level I). 111 of them (22.1%) had axillary lymph node metastasis, and 83 (16.5%) of them were treated with RT in our Institute. Sixty-one women were subjected to WBI. The coverage of axillary volumes by tangential fields is given in Table 4. There was a significant difference between the two plans regarding the coverage of the Level I axillary volume. HTgF increased the rate of complete coverage from 0% to 65.6% (40 of 61; p < 0.0001). Concerning the Level II volume, the rate of complete coverage with STgF or HTgF was 0% and 6.6% (4 of 61), respectively (p = 0.1198). The rate of "out of field" cases was very high with STgF, 72.1% (44 of 61), but "out of field" cases were not observed with HTgF irradiation (p < 0.0001). The coverage of the Level III volume was very poor

Table 1
Pathological characteristics of the primary breast tumour.

pT	n	%
pTis	104	11.8
pT1mi	3	0.3
pT1a	31	3.5
PT1b	95	10.8
pT1c	316	36.0
pT2	300	34.1
pT3	30	3.4
Grade (invasive tumours)		
I	180	23.4
II	370	48.1
III	219	28.5
Grade (in situ carcinomas)		
Low	28	26.9
Medium	50	47.8
High	26	25.3
Receptor status		
ER	751	80.5
PR	641	68.7
Her2	72	7.7
Molecular subtype		
Luminal A	438	59.4
Luminal B	171	23.2
Luminal B-Her2+	41	5.6
Non-luminal	73	9.9
Triple negative	14	1.9
Lymphovascular invasion		
Present	322	39.3
Not present	497	60.7
Histological type		
Invasive ductal carcinoma	643	73.1
Invasive lobular carcinoma	99	11.3
Other invasive	34	3.9
DCIS	75	8.5
LCIS	16	1.8
Other in situ	13	1.5
Palpability		
Palpable	499	55.9
Not palpable	393	44.1
Mitotic activity		
<11	539	67.0
11–20	157	19.5
20<	109	13.5
Type of breast surgery		
Mastectomy	371	39.8
Breast conserving surgery	562	60.2
SLN positivity		
SLN-negative patients	744	79.7
SLN-positive patients	189	20.3
Total removed SLNs	1538	na
SLNs removed per operation	1.6	na
ALND		
Total number of ALND	156	16.7
Total number of removed lymph nodes	2109	na
Lymph nodes removed per ALND	13.5	na
Positive lymph nodes per ALND	406	19.3

Table 2
Correlation between molecular subtype (column) and the location (row) of the primary breast tumour (p = 0.022).

	Luminal A		Luminal B		LumB – Her2		Non-luminal		Triple negative	
	n	%	n	%	n	%	n	%	n	%
Upper-outer	210	49.3	73	44.0	18	43.9	7	53.9	40	57.1
Upper-inner	65	15.3	39	23.5	5	12.2	4	30.8	9	12.9
Lower-outer	47	11.0	20	12.1	4	9.8	0	0	9	12.9
Lower-inner	36	8.5	13	7.8	7	17.1	0	0	1	1.4
Central	62	14.6	17	10.2	7	17.1	2	15.4	6	8.6
Axillary process	6	1.4	4	2.4	0	0	0	0	5	7.1

Table 3
Correlation between the location of the primary breast tumour (column) and the subregional location of the SLN (row) if intratumoural injections were used (p = 0.016) and distribution pattern and metastatic status of the SLN in the subregions of the axilla.

	Upper outer	Lower outer	Upper inner	Lower inner	Central	Axillary process	Stained & removed SLN	Positive SLN	Positivity rate
anterior	65 (34.2%)	13 (41.9%)	28 (53.9%)	16 (69.6%)	12 (54.5%)	5 (45.5%)	349 (39.9%)	73	20.9%
central	55 (28.9%)	8 (25.8%)	15 (28.8%)	6 (26.1%)	5 (22.7%)	1 (9.1%)	245 (28.0%)	53	21.6%
posterior	60 (31.6%)	7 (22.6%)	6 (11.5%)	1 (4.3%)	2 (9.1%)	4 (36.3%)	203 (23.2%)	43	21.2%
lateral	6 (3.2%)	3 (9.7%)	3 (5.8%)	0 (0.0%)	1 (4.6%)	1 (9.1%)	48 (5.5%)	11	22.9%
apical	4 (2.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (9.1%)	0 (0.0%)	30 (3.4%)	9	30.0%

Table 4
Coverage of axillary volumes by tangential fields (n = 61).

% (No.)		STgF	HTgF	p-value
Level I	Complete	0 (0)	65.6 (40)	<0.0001
	Partial	100.0 (61)	34.4 (21)	–
	Out of field	0 (0)	0 (0)	–
Level II	Complete	0 (0)	6.6 (4)	0.1198
	Partial	27.9 (17)	93.4 (57)	–
	Out of field	72.1 (44)	0 (0)	<0.0001
Level III	Complete	0 (0)	0 (0)	–
	Partial	8.2 (5)	90.2 (55)	–
	Out of field	91.8 (56)	9.8 (6)	<0.0001

STgF, standard tangential field; HTgF, high tangential field.

(rate of "out of field" with STgF or HTgF: 91.8% and 9.8%, p < 0.0001).

Discussion

The main objective of the study was to examine the presumable relationship between the quadrants of the breast and the subregions of the axilla and thus to describe a functional and morphologic lymphatic drainage pattern. Furthermore, the coverage of axillary volumes with tangential fields for WBI was also studied.

In summary, we did not find a significant correlation between the histopathological parameters of the primary breast cancer and the subregional location of the SLN. However, it is obvious from the data that the SLN is more than likely to be present in the anterior, posterior and central axillary subregions. Moreover, the SLN positivity rate in the lateral subregion (22.9%; n = 11) was not negligible. It is also clear from the data that upper-outer quadrant tumours spread least frequently to the anterior lymph nodes, while inner and central quadrant tumours have similar drainage patterns mainly to the anterior and central subregions.

There are several studies concerning the coverage of axillary lymph nodes from whole breast tangential field irradiation. Reed et al. [25] reported that using STgFs, no patient received complete coverage of the axillary Level I–II lymph node volume. They concluded that definitive irradiation of the Level I and II axillary lymph node regions required significant modification of the STgFs. Krasin et al. [26] showed that the use of STgFs does not therapeutically treat the regional lymph nodes. In their series, only 1 out of 25 patients had adequate coverage of the Level I region, and no patient had adequate coverage of Level II. Reznik et al. [27] observed that adequate coverage of Level I, defined when 95% of the volume received 95% of the dose, was achieved in none of the patients with normal tangents and in 6 patients (6 of 35) with high tangents. In a study by Orecchia et al. [28], the Level I nodes were only partially in the STgF, and the mean dose was only 48.7% of the prescribed dose. Our study was performed to address the issue of axillary volume coverage according to tangential field size. We showed that no patient had complete coverage of the Level I or Level II region with STgFs, and in 72.1% of the patients, the Level II volume was completely out of field. Using HTgF, 65.6% of the patients had complete coverage of Level I regions and the complete coverage rate was only 6.6% for Level II volume. The coverage of Level III region was very poor either with STgF (rate of out of field: 91.8%) or HTgF (rate of out of field: 9.8%).

Our results are consistent with the earlier studies that showed that STgF does not adequately cover the axillary volumes. With modern techniques, adequate coverage of the axillary volumes depends on the cranial field edge. Ohashi et al. [29] used 3D-CRT with a field-in-field technique, and half of the humeral head was inside the field. With this technique, even the dose to the Level III region was appropriate (V90 was 82.8%). In a study by Nagar et al. [30], when the tangential fields were modified to include Level I and II volumes, the mean dose (STgF vs. modified HTgF) increased from 35 Gy to 51 Gy and 11 Gy to 50 Gy, respectively. In patients studied by Belkacemi et al. [31], the STgF was defined with the cranial border set at 2 cm below the humeral head, while the HTgF consisted of a superior border placed at the inferior edge of the humeral head. The mean dose delivered to Level I with STgF or HTgF was 20 Gy and 33 Gy, respectively (p < 0.0001). We also used classical HTgF such as Belkacemi et al. [31], and the coverage of the Level I region was limited (complete coverage rate 65.6%). Attempts to increase the volume of complete coverage could induce a significant increase in lung dose. Alco et al. [32] suggested shaping the tangential field with multi-leaf collimators according to axillary level volumes to ensure complete coverage, but the inclusion of the axillary region in the target volume increased the irradiated lung volume. Mean lung dose was with the HTgF or multi-leaf collimators HTgF 6.5 and 9.6 Gy, respectively (p = 0.0001). To study the adequate coverage of the axilla, Levels I, II and III should be defined (delineated) by anatomical structures. STgFs provide limited coverage of the axilla, but HTgFs may provide complete coverage of Level I volume in some patients.

In our study, 9 (1.0%) positive SLNs were in the apical and 11 (1.3%) metastatic lymph nodes were in the lateral subregions. In total, 20 patients with positive lymph nodes (2.3% of our cases) would be left untreated if we applied tangential WBI to treat the axilla.

In our view, for the proper treatment of the axilla, an additional axillary and supraclavicular RT field is needed. This correlates with the findings of the Hungarian OTOASOR prospective randomised

clinical trial with axillary and supraclavicular field irradiation in the case of a metastatic SLN without ALND [33].

Applying the ARM technique, the lymph nodes stained with blue dye or radioisotope are preserved to prevent postoperative lymphedema. The subregional localisation of the ARM nodes has not yet been clearly identified, but it seems obvious that majority of the lymphatics draining the upper limb traverses deep in the axilla [17]. This was also confirmed by Ikeda et al. [34], who found ARM nodes in zones that correspond to mainly the lateral, apical and posterior axillary subregions.

In our study, 281 (32.1%) SLNs were found within one of these subregions, and 22.4% (n = 63) of them were positive. This means that 7.2% of all our cases had one positive lymph node in the expected ARM lymph node regions.

According to these results, due to the high rate of posterior subregional SLN drainage (21.8% n = 203) and SLN positivity (21.2%), not only the ALND but also the SLNB carry a high risk of a preserved positive lymph node and have a negative effect on the patient's successful treatment. This corresponds to the results that showed that the oncological safety of the ARM technique in patients with axillary lymph node metastasis from breast cancer is questionable [35,36], and proper indications, patient selection and further investigations are needed for the safe application of ARM [37].

Conclusion

Our findings suggest that there is no significant correlation between the histopathological parameters of the primary breast tumour and the subregional localisation of the SLN. The majority of SLNs are located in the anterior and central subregions.

When primary RT is used to treat the axilla, the contouring of the axillary lymph node levels is necessary for the proper design of the tangential field borders. Our analysis leads to the conclusion that STgF did not provide complete coverage of level I-II axillary lymph nodes. The use of high tangential fields is one means of improving axillary coverage with whole breast irradiation.

Tangential field WBI provides limited coverage of the axilla. Only 65.6% of our patients had complete Level I coverage with high tangential fields.

Moreover, using the ARM technique and leaving lymph nodes behind in the apical, lateral or posterior axillary subregions may leave behind up to 7.2% of metastatic lymph nodes, which may elevate the risk of possible understaging or undertreatment. In these cases, clipping the preserved lymph nodes is mandatory for adjuvant axillary RT.

Conflict of interest statement

All authors certify that there is no actual or potential conflict of interest in relation to this article.

Role of funding source statement

All authors certify that there were no funding sources; therefore, they did not play any role in data collection, analysis, interpretation, trial design, patient recruitment or any aspect pertinent to the study.

References

[1] Krag D, Weaver D, Ashikaga T, Moffat F, Klimberg VS, Shriver C, et al. The sentinel lymph node in breast cancer. A multicentre validation study. N Engl J Med 1998;339:941–6.
[2] Giuliano AE, Haigh PI, Brennan MB, Hansen NM, Kelley MC, Ye W, et al. Prospective observational study of sentinel lymphadenectomy without further axillary dissection in patients with sentinel node-negative breast cancer. J Clin Oncol (Italy) 2000 Jul;18(13):2553–9. Erratum in: J ClinOncol 2000 Nov 15;18(22):3877.
[3] Péley G, Sinkovics I, Liszkay G, Tóth J, Péter I, Farkas E, et al. The role of intraoperative gamma-probe-guided sentinel lymph node biopsy in the treatment of malignant melanoma and breast cancer. Orv Hetil 1999 Oct 17;140(42):2331–8.
[4] Coates AS, Winer EP, Goldhirsch A, Gelber RD, Gnant M, Piccart-Gebhart M, et al. Panel members tailoring therapies—improving the management of early breast cancer: St Gallen international expert consensus on the primary therapy of early breast cancer 2015. Ann Oncol 2015 Aug;26(8):1533–46. https://doi.org/10.1093/annonc/mdv221. Published online 2015 May 4.
[5] National ComprehensiveCancer Network (NCCN) clinical practice guidelines in clinical Oncology. Breast Canc 2017. Version 3, www.nccn.org. 11/10/17.
[6] Mátrai Z, Tóth L, Saeki T, Sinkovics I, Godény M, Takeuchi H, et al. The potential role of SPECT/CT in the preoperative detection of sentinel lymph nodes in breast cancer. Orv Hetil 2011 Apr 24;152(17):678–88. https://doi.org/10.1556/OH.2011.29077. Hungarian.
[7] Macéa JR, Fregnani JHTG. Anatomy of the thoracic wall, axilla and breast. Int J Morphol 2006;24(4):691–704.
[8] Berg JW. The significance of axillary node levels in the study of breast carcinoma. Cancer 1955;8:776–8.
[9] Ibusuki M, Yamamoto Y, Kawasoe T, Shiraishi S, Tomiguchi S, Yamashita Y, et al. Potential advantage of preoperative three-dimensional mapping of sentinel nodes in breast cancer by a hybrid single photon emission CT (SPECT)/CT system. Surg Oncol 2010 Jun;19(2):88–94. https://doi.org/10.1016/j.suronc.2009.04.001.
[10] Gallowitsch HJ, Kraschl P, Igerc I, Hussein T, Kresnik E, Mikosch P, et al. Sentinel node SPECT-CT in breast cancer. Can we expect any additional and clinically relevant information? Nuklearmedizin 2007;46(6):252–6.
[11] Giuliano AE, Hunt KK, Ballman KV, Beitsch PD, Whitworth PW, Blumencranz PW, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. J Am Med Assoc 2011 Feb 9;305(6):569–75. https://doi.org/10.1001/jama.2011.90.
[12] Giuliano AE, Ballman K, McCall L, Beitsch P, Whitworth PW, Blumencranz P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: long-term follow-up from the american college of surgeons Oncology group (alliance) ACOSOG Z0011 randomized trial. Ann Surg 2016 Sep;264(3):413–20. https://doi.org/10.1097/SLA.0000000000001863.
[13] Jagsi R, Chadha M, Moni J, Ballman K, Laurie F, Buchholz TA, et al. Radiation field design in the ACOSOG Z0011 (alliance) trial. J Clin Oncol 2014;32:3600–6.
[14] Nos C, Clough KB, Bonnier P, Lasry S, Le Bouedec G, Flipo B, et al. Upper outer boundaries of the axillary dissection. Result of the SENTIBRAS protocol: multicentric protocol using axillary reverse mapping in breast cancer patients requiring axillary dissection. Eur J Surg Oncol 2016 Dec;42(12):1827–33. https://doi.org/10.1016/j.ejso.2016.07.138. Epub 2016 Aug 26.
[15] Tummel E, Ochoa D, Korourian S, Betzold R, Adkins L, McCarthy M, et al. Does axillary reverse mapping prevent lymphedema after lymphadenectomy? Ann Surg 2017 May;265(5):987–92. https://doi.org/10.1097/SLA.0000000000001778.
[16] Beek MA, Gobardhan PD, Schoenmaeckers EJ, Klompenhouwer EG, Rutten HJ, Voogd AC, et al. Axillary reverse mapping in axillary surgery for breast cancer: an update of the current status. Breast Canc Res Treat 2016 Aug;158(3):421–32. https://doi.org/10.1007/s10549-016-3920-y. Epub 2016 Jul 21.
[17] Han C, Yang B, Zuo WS, Zheng G, Yang L, Zheng MZ. The feasibility and oncological safety of axillary reverse mapping in patients with breast cancer: a systematic review and meta-analysis of prospective studies. PloS One 2016 Feb 26;11(2). https://doi.org/10.1371/journal.pone.0150285. eCollection 2016. e0150285.
[18] National comprehensive cancer network (NCCN) clinical practice guidelines in clinical Oncology. Breast Canc 2013. Version 1, www.nccn.org. 02/01/13.
[19] Senkus E, Kyriakides S, Penault-Llorca F, Poortmans P, Thompson A, Zackrisson S, et al., ESMO GuidelinesWorking Group. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. vi7-23 Ann Oncol 2013 Oct;24(6). https://doi.org/10.1093/annonc/mdt284. Epub 2013 Aug 22.
[20] Recommendations of the 2nd breast cancer consensus conference (Kecskemét, november 8-9, 2009). Magy Onkol 2010 Sep;54(3).
[21] Cserni G, Francz M, Járay B, Kálmán E, Kovács I, Kulka J, et al. Az emlőrák patológiai diagnosztikája, feldolgozása és kórszövettani leletezése. Magy Onkol 2010 Sep;54(3):217–26.
[22] Lester SC, Bose S, Chen YY, Connolly JL, de Baca ME, Fitzgibbons PL, et al. Members of the Cancer Committee, College of American Pathologists. Protocol for the examination of specimens from patients with invasive carcinoma of the breast. Arch Pathol Lab Med 2009 Oct;133(10):1515–38. https://doi.org/10.1043/1543-2165-133.10.1515.
[23] White J,Tai A, Arthur D, Buchholz T, MacDonald S, Marks L, Pierce L, et al. Breast Cancer Atlas for Radiation Therapy Planning: Consensus Definition. RTOG website: www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx.
[24] Hammer O, Harper DAT, Ryan PD. PAST: paleontological Statistics software package for education and dataanalysis. Palaeontol Electron 2001;4(1):9.

[25] Reed DR, Lindsley SK, Mann GN, Austin-Seymour M, Korssjoen T, Anderson BO, et al. Axillary lymph node dose with tangential breast irradiation. Int J Radiat Oncol Biol Phys 2005;61:358–64.
[26] Krasin M, McCall A, King S, Olson M, Emami B. Evaluation of a standard breast tangent technique: a dose-volume analysis of tangential irradiation using three-dimensional tools. Int J Radiat Oncol Biol Phys 2000;47:327–33.
[27] Reznik J, Cicchetti MG, Degaspe B, Fitzgerald TJ. Analysis of axillary coverage during tangential radiation therapy to the breast. Int J Radiat Oncol Biol Phys 2005;61:163–8.
[28] Orecchia R, Huscher A, Leonardi MC, Gennari R, Galimberti V, Garibaldi C, et al. Irradiation with standard tangential breast fields in patients treated with conservative surgery and sentinel node biopsy: using a three-dimensional tool to evaluate the first level coverage of the axillary nodes. Br J Radiol 2005;78:51–4.
[29] Ohashi T, Takeda A, Shigematsu N, Fukada J, Sanuki N, Amemiya A, et al. Dose distribution analysis of axillary lymph nodes for three-dimensional conformal radiotherapy with a field-in-field technique for breast cancer. Int J Radiat Oncol Biol Phys 2009;73:80–7.
[30] Nagar H, Zhou L, Biritz B, Sison C, Chang J, Smith M, et al. Is there a tradeoff in using modified high tangent field radiation for treating an undissected node-positive axilla? Clin Breast Canc 2014;14:109–13.
[31] Belkacemi Y, Allab-Pan Q, Bigorie V, Khodari W, Beaussart P, Totobenazara JL, et al. The standard tangential fields used for breast irradiation do not allow optimal coverage and dose distribution in axillary levels I-II and the sentinel node area. Ann Oncol 2013;24:2023–8.
[32] Alço G, Iğdem SI, Ercan T, Dinçer M, Sentürk R, Atilla S, OralZengin F, et al. Coverage of axillary lymph nodes with high tangential fields in breast radiotherapy. Br J Radiol 2010;83:1072–6.
[33] Sávolt Á, Péley G, Polgár C, Udvarhelyi N, Rubovszky G, Kovács E, et al. Eight-year follow up result of the OTOASOR trial: the Optimal Treatment of the Axilla–Surgery or Radiotherapy after positive sentinel lymph node biopsy in early-stage breast cancer: a randomized, single centre, phase III, non-inferiority trial. Eur J Surg Oncol 2017 Apr;43(4):672–9. https://doi.org/10.1016/j.ejso.2016.12.011. Epub 2017 Jan 16.
[34] Ikeda K, Ogawa Y, Komatsu H, Mori Y, Ishikawa A, Nakajima T, et al. Evaluation of the metastatic status of lymph nodes identified using axillary reverse mapping in breast cancer patients. World J Surg Oncol 2012 Nov 1;10:233. https://doi.org/10.1186/1477-7819-10-233.
[35] Bedrosian I, Babiera GV, Mittendorf EA, Kuerer HM, Pantoja L, Hunt KK, et al. A phase I study to assess the feasibility and oncologic safety of axillary reverse mapping in breast cancer patients. Cancer 2010 Jun 1;116(11):2543–8. https://doi.org/10.1002/cncr.25096.
[36] Schunemann Jr E, Dória MT, Silvestre JB, Gasperin Jr P, Cavalcanti TC, Budel VM. Prospective study evaluating oncological safety of axillary reverse mapping. Ann Surg Oncol 2014 Jul;21(7):2197–202. https://doi.org/10.1245/s10434-014-3626-5. Epub 2014 Mar 6.
[37] Rubio IT, Luiten EJT, Klimberg VS. Axillary reverse mapping: ARM. In: Wyld L, Markopoulos C, Leidenius M, Senkus-Konefka E, editors. Breast cancer management for surgeons. Switzerland: Springer International Publishing; 2018. p. 303–12.

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COMMENTARY

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Clinicopathological correlations of areola-sparing mastectomies versus nipple-sparing mastectomies: Analysis of the oncological and cosmetic importance of the components of the nipple-areola complex

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In recent years, nipple-sparing mastectomy (NSM) has become the primary mastectomy technique.[1] The oncological and cosmetic importance of the nipple and separately the pigmented areola should be better understood by the modern breast oncoplastic surgery.

The aim of this study was to perform a long-term comparison of the oncological safety and cosmetic outcomes of areola-sparing mastectomy (ASM) with those of NSM.

This single-center retrospective comparative study was performed between April 2013 and December 2018 at the National Institute of Oncology, Hungary, based on the prospectively led institutional database.

The diagnosis of breast cancer, staging examinations, oncological treatments, and follow-up was performed according to the institutional protocol based on the actual ESMO guideline.

The indication for mastectomy was either therapeutic for breast cancer or prophylactic for patients with BRCA mutation. ASM was the technique first applied, while it was subsequently replaced by NSM after its international acceptance.

All procedures in both groups were performed with the same technique, applying the same type of submusculary placed tissue expander with delayed-immediate implant-based breast reconstruction.

For the axillary staging, sentinel lymph node biopsy was performed according to the criteria of the ACOSOG Z0011 trial.

Postoperative complications were assessed by applying the Clavien-Dindo Classification system.

For the assessment of the esthetic outcomes, a 5-point Likert scale was applied.

The BREAST-Q reconstruction module version 2.0 postoperative questionnaire was applied at 6 months after surgery.

All the collected data were statistically analyzed using Statistica 12.0 software (StatSoft, Tulsa, OK) or PAST version 1.86b.

After the exclusion of 24 patients, a total of 134 and 93 patients were enrolled in the study.

Detailed patient and tumor characteristics are summarized in Table 1.

The recorded early postoperative complications in the two groups are summarized in Table 2.

At the mean follow-up of 45 months, there was no significant difference in the disease-free survival (DSF) (P = .762) and overall survival (OS) (P = .601) between the two groups [Figure 1].

Both groups had the same objective esthetic outcomes by the 5-point Likert scale system [Table 3].

The results of the corresponding BREAST-Q domains showed no significant difference between ASM and NSM patients [Table 3].

This study revealed that preservation of the nipple does not make oncological difference, while preserving breast projection and pigmented areola seems to have the same importance than the

TABLE 1 (A) Patient characteristics (B) Characteristics of the primary breast tumor

(A)			
	ASM	**NSM**	***P***
Number of patients	134	93	
Age (y)			
Median (min.–max.)	41 (26-64)	40 (26-70)	.365
BMI (kg/m^2)			
Mean ± SD	21.6 ± 3.1	21.2 ± 3.4	.285
Cup size	n (%)	n (%)	
A	23 (17.2)	7 (7.5)	.003
B	75 (55.9)	62 (66.7)	
C	25 (18.7)	24 (25.8)	
D	11 (8.2)	0 (0.0)	
Indication	n (%)	n (%)	
Therapeutic	89 (66.4)	85 (91.4)	1.2×10^{-5}
Prophylactic	45 (33.6)	8 (8.6)	
Operative duration (minutes)			
Median (min.–max.)	80 (50-150)	76 (43-120)	.431
Neoadjuvant	n (%)	n (%)	
Chemotherapy	20 (22.5)	9 (10.6)	.244
Initiation of adjuvant therapy (weeks)			
Median (min.–max.)	7.4 (4.6-11.9)	8.1 (4.1-12.0)	.124
Adjuvant	n (%)	n (%)	
Chemotherapy/Biological therapy			.068
Yes	34 (25.4)	19 (20.4)	
No	59 (44.0)	61 (65.6)	
Not reported	41 (30.6)	13 (14.0)	
Radiotherapy			
Yes	32 (23.9)	27 (29.0)	.993
No	63 (47.0)	53 (57.0)	
Not reported	39 (29.1)	13 (14.0)	
Endocrine therapy			
Yes	46 (34.3)	61 (65.6)	.001
No	45 (33.6)	21 (22.6)	
Not reported	43 (32.1)	11 (11.8)	

(B)			
	ASM	**NSM**	
Pathological TNM	**n = 89 (therapeutic)**	**n = 85 (therapeutic)**	***P***
pT	n (%)	n (%)	.026
pTis	5 (5.6)	6 (7.1)	
pT1	37 (41.6)	33 (38.8)	
pT2	23 (25.8)	19 (22.3)	
pT3	4 (4.5)	18 (21.1)	
pN	n (%)	n (%)	.900
pN0	47 (52.8)	53 (62.3)	

(Continues)

TABLE 1 (Continued)

(B)			
	ASM	NSM	
Pathological TNM	n = 89 (therapeutic)	n = 85 (therapeutic)	*P*
pN1	18 (20.2)	19 (22.3)	
pN2	3 (3.4)	2 (2.4)	
pN3	1 (1.1)	2 (2.4)	
ypT	n (%)	n (%)	
ypT0	5 (5.6)	4 (4.7)	
ypT1	9 (10.2)	2 (2.4)	
ypN2	4 (4.5)	2 (2.4)	
ypN3	2 (2.2)	1 (1.2)	
ypN	n (%)	n (%)	
ypN0	11 (12.4)	6 (7.0)	
ypN1	7 (7.9)	2 (2.4)	
ypN2	1 (1.1)	0 (0)	
ypN3	1 (1.1)	1 (1.2)	
Grade (invasive breast cancer)			
I	16 (18.0)	11 (12.9)	.435
II	34 (38.2)	40 (47.1)	
III	39 (43.8)	34 (40.0)	
Receptor status			
ER			.004
Positive	60 (44.8)	59 (63.4)	
Negative	32 (23.9)	10 (10.8)	
Not reported	42 (31.3)	24 (25.8)	
PR			.008
Positive	56 (41.8)	56 (60.2)	
Negative	35 (26.1)	13 (14.0)	
Not reported	43 (32.1)	24 (25.8)	
Her2			.951
Positive	20 (14.9)	15 (16.1)	
Negative	71 (53.0)	52 (55.9)	
Not reported	43 (32.1)	26 (28.0)	
Histological type			
Invasive ductal carcinoma	74 (83.2)	60 (70.6)	.349
Invasive lobular carcinoma	5 (5.6)	11 (12.9)	
Other invasive	4 (4.5)	6 (7.1)	
DCIS	5 (5.6)	6 (7.1)	
LCIS	1 (1.1)	2 (2.3)	
Nipple—tumor distance (cm)			
Median (min.–max.)	2.7 (0.6-7.0)	3.1 (0.7-7.0)	.497
Follow-up 45 mo (range: 20.1-82.7)			
Local recurrence	3 (3.4)	2 (2.4)	
Distant metastatic disease	5 (5.6)	1 (1.2)	

(Continues)

TABLE 1 (Continued)

(B)			
	ASM	NSM	
Pathological TNM	**n = 89 (therapeutic)**	**n = 85 (therapeutic)**	***P***
Distant metastases-related death	2 (2.2)	1 (1.2)	
Axillary surgery			
Sentinel lymph node biopsy	64 (71.9)	62 (72.9)	.656
Axillary lymph node dissection	23 (25.9)	19 (22.4)	
No axillary surgery	2 (2.2)	0	
Not reported	0	4 (4.7)	

TABLE 2 Early postoperative complications based on the Clavien-Dindo Classification

	ASM	NSM	
	134 n (%)	**93 n (%)**	***P***
Grade I	12 (9.0)	9 (9.7)	
infection	4 (3.0)	3 (3.2)	
seroma	2 (1.5)	2 (2.1)	
partial skin/ NAC necrosis	3 (2.2)	2 (2.1)	
rippling	2 (1.5)	1 (1.1)	
wound dehiscence	1 (0.7)	1 (1.1)	
Grade II	3 (2.2)	1 (1.1)	
infection	2 (1.5)	0 (0.0)	
chronic seroma	1 (0.7)	1 (1.1)	
Grade III	3 (2.2)	2 (2.1)	
hematoma	2 (1.5)	1 (1.1)	
implant loss	1 (0.7)	1 (1.1)	
Overall	18 (13.4)	12 (12.9)	.908

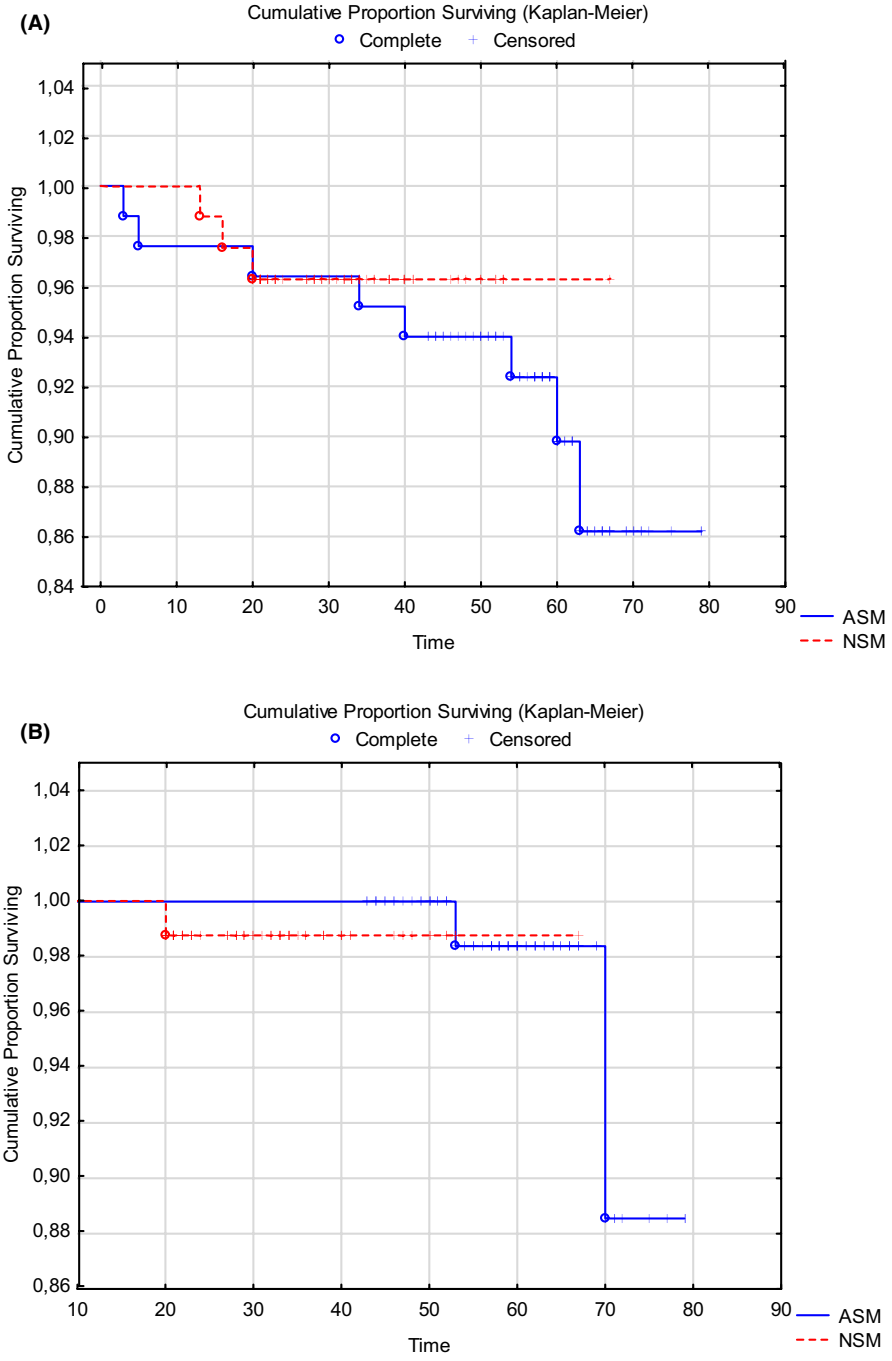

FIGURE 1 Kaplan-Meier curve showing (A) DSF and (B) OS of the two groups

TABLE 3 Results of the Likert scale system (A) and the BREAST-Q postoperative questionnaire (B)

(A)		
	ASM median (range)	NSM median (range)
Likert score	4.1 (2-5)	4.3 (2-5)

(B)			
	ASM mean ± SD	NSM mean ± SD	*P*
Satisfaction with breasts	64.9 ± 21.2	67.8 ± 17.2	.691
Psychosocial well-being	68.4 ± 18.4	72.4 ± 17.5	.123
Physical well-being	80.0 ± 14.0	76.5 ± 15.5	.232
Sexual well-being	59.1 ± 18.3	54.0 ± 20.9	.252

complex NAC itself. Therefore, ASM could be a suitable treatment option, if NSM is not oncologically feasible.

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REFERENCES

1. Weber W, Haug M, Kurzeder C, et al. Oncoplastic breast consortium consensus conference on nipple-sparing mastectomy. *Breast Cancer Res Treat*. 2018;172(3):523-537.

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III.

A magyar emlőrákos betegek igényei a korszerű onkoplasztikus emlősebészeti ellátásra

500 beteg kérdőíves vizsgálata

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Bevezetés: A korszerű onkoplasztikus emlősebészet következményeként megjelenő jelentős emlőrekonstrukciós igény számos rendszerszintű kérdést vet fel. Vizsgálatra és szabályozásra várnak az onkoterápiák hatására és az idő múlásával bekövetkező esztétikai változások, illetve hosszú távú szövődmények miatti korrekciós műtétek indikációi; meghatározandó a helyreállító beavatkozások optimális és maximális száma, az elérni kívánt esztétikai végcél és az ezekhez szükséges emlősebészeti kapacitások, valamint finanszírozás.
Célkitűzés: A jelen vizsgálat célja, hogy kérdőíves vizsgálattal felmérje a magyar emlőrákos populáció korszerű emlőrekonstrukciós igényeit és véleményét.
Anyag és módszer: A vizsgálatba 500, mastectomián és azonnali vagy halasztott-azonnali emlőrekonstrukción átesett nőbeteg került bevonásra. Tizenegy kérdésből álló kérdőív segítségével történt az emlő rekonstrukciójához való ismereteknek és személyes viszonyulásnak, az esztétikai végeredménnyel és az ellátás szakmai színvonalával kapcsolatos elvárásoknak, továbbá az ellátórendszerrel és a finanszírozással kapcsolatos igényeknek a felmérése, majd elvégeztük az eredmények biostatisztikai elemzését.
Eredmények: A betegek medián életkora 47 év (min.–max.: 26–73) volt, döntő részük (59%; n = 294) házas volt, és 52% (n = 260) rendelkezett egyetemi végzettséggel. A betegek 70%-a (n = 348) az emlő-helyreállítás eredményeként mezítelenül is nagyjából egyforma emlőket szeretett volna. Ehhez 43%-uk (n = 217) maximum kettő, 37%-uk (n = 184) maximum három-négy műtétet vállalna. A felmérésben részt vettek 44%-a (n = 220) szerint az egészségbiztosítónak három-négy rekonstrukciós beavatkozást kellene támogatnia. A betegek 86%-a (n = 430) a daganatos emlő korszerű sebészi kezelését speciálisan képzett emlősebészre bízná.
Következtetés: Az emlőrák modern onkoplasztikus sebészi ellátása összetett, rendszerszintű kérdéseket vet fel. Az emlőrákos betegek jól képzett emlősebészeket szeretnének, akik az emlőrák korszerű sebészi kezelésén túl mastectomia esetén az egészségbiztosító által támogatott formában, maximum két műtéttel képesek magas esztétikai eredménnyel az emlők helyreállítására.
Orv Hetil. 2020; 161(29): 1221–1228.

Kulcsszavak: onkoplasztikus emlőrekonstrukció, emlőrák, mastectomia, finanszírozás, kérdőíves vizsgálat

Assessing the needs of Hungarian breast cancer patients for modern oncoplastic breast surgical treatment

Questionnaire study of 500 patients

Introduction: The significant need for breast reconstruction resulting from the spread of oncoplastic breast surgery raises a number of systemic issues. Clarification and regulation of the indications are needed for aesthetic changes of the reconstructed breast due to oncotherapy treatments, ageing and technical problems of implants; a number of operations, targeted aesthetic goals as well as surgical capacities and financial background should also be determined.

Aim: Our aim was to conduct a survey on the opinions and needs of the Hungarian breast cancer population about a modern breast reconstruction system.
Patient and method: A study was conducted enrolling 500 patients who underwent mastectomy with immediate or delayed reconstruction. A structured questionnaire containing eleven questions was used to measure the attitude for loss and reconstruction of breast, the expectation of cosmetic outcome and qualification of the operating surgeon and the needs relating to the health system and funding.
Results: The median age was 47 years (min.–max.: 26–73), 59% (n = 294) was married and 52% (n = 260) had graduated in university. The majority of women (70%; n = 348) would like to have nakedly also similar breasts after the reconstruction process. To achieve this, 43% (n = 217) and 37% (n = 184) would undergo maximum two or four procedures, respectively, supported by the national health insurance company. 86% (n = 430) would like to choose qualified breast surgeon for her treatment.
Conclusion: The modern oncoplastic treatment raises complex, systemic issues. Women with breast cancer would like to have qualified breast surgeons restoring their breasts by two operations, all funded by the national health insurance company.

Keywords: oncoplastic breast reconstruction, breast cancer, mastectomy, questionnaire study, financing

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Rövidítések

BRESO = (Breast Surgical Oncology) mellsebészeti onkológia projekt; BU = (breast unit) emlőterápiás szervezeti egység; CEEBCSC = (Central-Eastern European Breast Cancer Surgical Consortium) Kelet-közép-európai Emlőráksebészeti Konzorcium; EBCC = (European Breast Cancer Conference) Európai Emlőrák Konferencia; ECIBC = (European Commission Initiative on Breast Cancer) „Európai összefogás a mellrák ellen!"; EORTC = (European Organization for the Research and Treatment of Cancer) Európai Rákkutató és Terápiás Szervezet; ESO = (European School of Oncology) Európai Onkológiai Iskola; ESSO = (European Society of Surgical Oncology) Európai Sebészeti Onkológiai Társaság; EUBREAST = European Breast Cancer Research Association of Surgical Trialists; EUSOMA = European Society of Mastology; G.Re.T.A. = Group for Reconstructive and Therapeutic Advancements; NEAK = Nemzeti Egészségbiztosítási Alapkezelő; OOI = Országos Onkológiai Intézet; SD = standard deviáció; UEMS = (European Union of Medical Specialists) Európai Szakorvosi Szövetség

A Nemzeti Rákregiszter adatai alapján hazánkban évente 8300–8500 új emlőrákos megbetegedést diagnosztizálnak, és évente sajnálatosan mintegy 2200 nő hal bele a betegségbe [1]. Az emlőrák incidenciája Európában lassan, de emelkedik. Kontinensünkön még a hasonló gazdasági helyzetű országok esetében is észlelhető érdemi különbség az emlőrákellátási rendszerekben [2, 3]. A speciális igényű onkológiai ellátás egyenlőtlenségei miatt 1998-ban Firenzében az első Európai Emlőrák Konferencián (EBCC) a multidiszciplináris emlőterápiás szervezeti egységek, az ún. „breast unitok" (BU-ok) feltétel- és minőségbiztosítási elvárásai kerültek meghatározásra [4]. A European Organization for the Research and Treatment of Cancer (EORTC) és a European Society of Mastology (EUSOMA) munkacsoportja megalkotta az emlőrák gyógyításával foglalkozó szakorvosokkal szemben támasztott alapkövetelményeket, melyek lehetővé tették a szakellátás minőségbiztosítási kontrollját [5]. A European Union of Medical Specialists (UEMS) és a European Society of Surgical Oncology (ESSO) 2010-ben emlősebészeti licencvizsgát hozott létre, amelynek vizsgáztatási folyamatában az Országos Onkológiai Intézet (OOI) és a szerzők évek óta aktív szerepet vállalnak. A második Európai Emlőrák Konferencián a „Brüsszeli Nyilatkozatban" (The Brussels Statement) az akkreditációs feltételrendszer került létrehozásra [6]. 2019-ben az emlősebészeti szakismeretek intézeti, osztályos vagy egyéni szintű egységes európai akkreditációjára az ESSO, a UEMS, a European Breast Cancer Coalition (Europa Donna), a European School of Oncology (ESO), a European Breast Cancer Research Association of Surgical Trialists (EUBREAST), a European Commission Initiative on Breast Cancer (ECIBC), a magyar kezdeményezésre létrejött Central-Eastern European Breast Cancer Surgical Consortium (CEEBCSC) és a Group for Reconstructive and Therapeutic Advancements (G.Re.T.A.) életre hívta a Breast Surgical Oncology (BRESO-) projektet [7]. A BRESO-projekt megalkotta a teljes kontinensre kiterjedő, standardizált emlősebészeti curriculumot és minőségbiztosítási rendszert, valamint annak akkreditációs feltételeit. A felsorolt nyilatkozatok hatására az Európai Parlament 2003-ban állásfoglalást adott ki, amely egyértelműen támogatta a minősített BU-ok intézményrendszerének európai elterjesztését, illetve 2013-ban megjelent a komplexebb ellátásra alkalmas emlőközpontok (breast centres) minimálfeltételeinek összefoglalója [8].

Az akkreditált BU-minősítés követelménye, hogy az adott centrumban a multidiszciplináris emlőterápiás bizottsági döntést követően évente legalább 150, újonnan diagnosztizált emlőrákos beteg komplex onkológiai kezelése történjen, folyamatosan frissített szakmai protokollok alapján. Az akkreditáció elengedhetetlen része a standardizált adatbázis kialakítása és vezetése, a lakossági mammográfiás szűrés biztosítása, valamint oktatási és egyéb tudományos kutatási tevékenységek ellátása is [8–10]. A BU-rendszer hazai helyzetéről és eredményeiről munkacsoportunk 2016-ban számolt be az *Orvosi Hetilap*ban [11].

A korszerű onkoplasztikus emlősebészet elmúlt évtizedekben történő gyors elterjedése következtében napjainkban nemcsak az emlőtumor eltávolítása, hanem a nőiesség szimbólumának számító emlők esztétikailag teljes megőrzése vagy postmastectomiás helyreállítása is a sebészeti szakellátás alapvető része [12–14]. Minden olyan emlődaganatos nő számára, akinél sajnálatosan mastectomia szükséges, ellenjavallatok hiányában fel kell ajánlani és biztosítani kell tudni az emlő rekonstrukciójának lehetőségét [15]. A fentiek miatt megjelenő emlőrekonstrukciós igény már önmagában nemcsak az emlő- és plasztikai sebészeket állítja kihívás elé, hanem rendszerszintű feladatokat ró minden európai országra.

Az alap helyreállító sebészeti feladatokon túl azonban szakmailag tisztázásra várnak az onkoplasztikus működésből eredő további emlősebészeti feladatok és indikációk, amelyek értékelése és szabályozott ellátása még a jelenleg már fejlett emlősebészeti ellátórendszereknek is számos ismeretlen faktort tartalmaz. A primer, rendszerszinten tömegeken végzett emlő-helyreállítás másodlagos feladatköre jelentősen kibővül. Új ellátási feladatok jelennek meg, melyek szintén az onkológiai ellátórendszert terhelik, mint – a hosszan (akár 5–10 évig) tartó endokrin kezelések következtében ismerten fellépő testsúlygyarapodásból [16–18] vagy a kiváló túlélési eredmények alapján az életkor előrehaladásával („aging") [19–21], illetve az onkoterápiás beavatkozások (például radioterápia) következtében [22] – a rekonstruált emlőn vagy a szimmetrizált ellenoldali emlőn jelentkező esztétikai változások és az ezekből eredő további lehetséges műtéti indikációk. A fenti új szakmai elvárásokon túl a szükséges emlősebészeti ellátórendszer humánerőforrás- és műtéti kapacitásainak meghatározásához számba kell venni az onkológiai emlőrekonstrukció során beültetett implantátumok hosszú távú technikai problémáiból eredő szövődmények (például implantátumruptura), illetve állapotok (például kapszuláris kontraktúra) szakellátásának igényét is, valamint az ellenoldali emlő szimmetrizációjának megváltozásából eredő további lehetséges műtéti korrekciók tömeges jelentkezésének kérdéskörét is. Mindezen szakmai tények figyelembevételével szükséges meghatározni az onkoplasztikus rekonstrukciós beavatkozásokkal elérni kívánt, reális esztétikai végcélt, illetve az ehhez szükséges, az onkológiai ellátórendszer keretein belül elvégezhető helyreállító műtétek optimális, illetve maximális számát. Az onkoplasztikus ellátás mint standard emlőráksebészeti ellátás tehát a primer onkológiai és helyreállító sebészeten túlmutató, sokszor szakmailag nehezen meghatározható szubjektív indikációkat vagy élethosszig tartó kozmetikai változások lehetséges korrekcióit is magában foglalja.

Az új emlősebészeti igények megismerése, tudományos alapú meghatározása és reális értékelése nélkülözhetetlen alap a szükséges feltételrendszer kialakításához. Jelenleg hazánkban a Nemzeti Egészségbiztosítási Alapkezelő (NEAK) az eltávolított daganatos emlő helyreállítását minden magyar biztosított számára finanszírozza, ugyanakkor ezen összetett új indikációkat jelenleg rendszerszinten nem ismeri fel, és ennek megfelelően szakmailag nem is kezeli. Az emlő-helyreállítás jelentős vívmány az emlőrákban szenvedő magyarok számára, de a rekonstrukciós igény emelkedése és az indikációs kör kibővülése esetén e népbetegség magas esetszámánál a közeljövőben lavinaszerű, szabályozatlan helyzet alakulhat ki, amelynek megelőzése szakmai ismereteket és tervezést igényel.

A fentiek alapján a jelen kérdőíves prospektív vizsgálat célja a korszerű onkoplasztikus ellátással kapcsolatban a betegek igényeinek és elvárásainak megismerése és tudományos igényű elemzése.

Módszer

A vizsgálatba az OOI Emlő-Lágyrész Daganatsebészeti Osztályán 2015. január és 2017. december között 500, emlőrák miatt mastectomiára szoruló nőbeteg került bevonásra, akiknél vagy a daganatos emlő eltávolításával egy időben (azonnali) vagy egy időben megkezdett (például szövettágító expander beültetésével) és második lépésben befejezett (halasztott-azonnali emlő-helyreállítás) emlőrekonstrukció történt. A vizsgálatot és a kérdőívet az intézet Etikai Bizottsága jóváhagyta. A közlemény nem sérti a helsinki, illetve a tokiói deklaráció követelményeit [23].

A betegek kivizsgálása és kezelése minden esetben az OOI által alkalmazott aktuális nemzetközi és hazai irányelvek szerint történt [24–26]; a műtéteket az intézeti Emlőrák Terápiás Bizottság döntését követően tapasztalt és nemzetközi szakvizsgával minősített emlősebészek és plasztikai sebészek végezték.

A kérdőívek az emlőműtétet megelőző napon kerültek kiosztásra a betegeknek, kitöltésük a beavatkozás előtt történt önkéntesen és anonim módon.

Az életkorra, a legmagasabb iskolai végzettségre és a családi állapotra irányuló kérdéseket követően a kérdőív további tizenegy, strukturált kérdést tartalmazott. A kérdések a betegeknek az emlő elvesztésével kapcsolatos érzelmi és pszichés állapotára és viszonyulására, illetve az emlő helyreállításával kapcsolatos ismereteikre és akaratukra, valamint a rekonstruált emlők esztétikai végeredményével és az operáló orvos szakképzettségével kapcsolatos elvárásaikra, továbbá az emlősebészeti ellátással

1. táblázat | Az onkoplasztikus ellátás felmérését vizsgáló strukturált kérdőív és a kapott válaszok

1. Mennyire zavarja az emlő elvesztése vagy esztétikai deformitása egy 1-től 10-ig terjedő skálán? (1: nem zavar – 10: rettentően zavar)			
n	Átlag	Medián	Standard deviáció
495	8	9	3
Hiányzó adat = 5 (1%)			
2. Mikor történik Önnél az emlő rekonstrukciója?			
A daganat eltávolítása után hónapokkal, évekkel.		A daganat eltávolításával egy időben.	
167 (33%)		307 (61%)	
Hiányzó adat = 26 (5%)			
3. Ön reálisan mit vár az emlő helyreállításától?			
Legyen „valamiféle” emlőm.	Legyen melltartóban szép dekoltázsom.	Legyen szebb emlőm, mint a betegség előtt.	Legyenek tökéletes emlőim.
46 (9%)	194 (39%)	140 (28%)	99 (20%)
Hiányzó adat = 21 (4%)			
4. Önnek reálisan milyen mértékű szimmetria fogadható el az emlő-helyreállítás végén?			
A természetes emlőim sem voltak szimmetrikusak, ezért nem fontos, ha nem egyformák a rekonstruált emlőim.	Legyenek ruhában vagy melltartóban nagyjából egyformák a rekonstruált emlőim.	Legyenek mezítelenül is nagyjából egyformák a rekonstruált emlőim.	Csak a teljes szimmetria az elfogadható számomra.
12 (2%)	105 (21%)	348 (70%)	32 (6%)
Hiányzó adat = 3 (1%)			
5. Maximum hány műtétet vállalna altatásban az emlők helyreállításához?			
Maximum kettőt.	Maximum 3-4-et.	Maximum 5-6-ot.	Akármennyit.
217 (43%)	184 (37%)	25 (5%)	67 (13%)
Hiányzó adat = 7 (1%)			
6. Ön szerint hány rekonstrukciós műtét „állami” finanszírozása jogos egy általános biztosítottnak, ha ismert, hogy a lehetőségek nem végtelenek?			
Maximum kettőnek.	Maximum 3-4-nek.	Akármennyinek.	
107 (21%)	220 (44%)	157 (31%)	
Hiányzó adat = 16 (3%)			
7. Ön szerint a most helyreállítandó/helyreállított emlők, ha idővel például az öregedéssel megváltoznak, akkor az:			
nem indokol további helyreállítást, mert természetes folyamat.	természetes folyamat, amely a jövőben egyéni esztétikai sebészeti kérdés.	évtizedek múlva is rekonstrukciós sebészetnek és nem esztétikai műtétnek számít.	
71 (14%)	275 (55%)	139 (28%)	
Hiányzó adat = 15 (3%)			
8. Beleegyezne-e abba, hogy az Ön emlő-helyreállítását ne plasztikai sebész szakorvos, hanem általános sebész szakorvos végezze?			
Igen.		Nem.	
40 (8%)		448 (90%)	
Hiányzó adat = 12 (2%)			
9. Ön szerint a daganatos emlők korszerű sebészeti ellátását (onkoplasztika, emlő-helyreállítás stb.) ki végezze hazánkban?			
Általános sebész, mint hazánkban ma a legtöbbször.	Nőgyógyász, mint hazánkban ma néhány helyen.	Plasztikai sebész.	Speciálisan felkészült emlősebész, ha kell, plasztikai sebészt is bevonva.
5 (1%)	3 (1%)	54 (11%)	430 (86%)
Hiányzó adat = 8 (2%)			
10. Ön szerint mennyire fogadható el, hogy hazánkban a XXI. században csak egy-két kórházban van speciálisan felkészült, korszerű emlősebészet?			
Így jó, ahogy van.	Sajnálatos, de ez van.	Nagyon sajnálatos, aki jobbat akar, az elmegy magánellátásba.	Elfogadhatatlan, biztosítani kell a korszerű, specializált emlő-sebészetet.
2 (1%)	51 (10%)	46 (9%)	394 (79%)
Hiányzó adat = 7 (1%)			
11. Ön szerint gyógyulását érdemben befolyásolja-e, hogy emlősebész specialista operálja?			
Nem befolyásolja.	Befolyásolja.	Nagyon befolyásolja.	Az egyik legfontosabb.
14 (3%)	54 (11%)	111 (22%)	316 (63%)
Hiányzó adat = 5 (1%)			

szemben rendszerszinten támasztott igényekre és azok feltételrendszerére (például finanszírozás) vonatkoztak *(1. táblázat)*.

A kapott válaszok adatai, valamint azok szociális összefüggései Fisher-egzakt teszt és khi-négyzet-próba alkalmazásával kerültek biostatisztikai elemzésre. A 0,05 alatti p-érték számított szignifikánsnak.

A statisztikai analízis Statistica 12.0 (StatSoft, Tulsa, OK, Amerikai Egyesült Államok) és PAST version 1.86b szoftverek segítségével történt [27].

Eredmények

A nőbetegek medián életkora 47 év (min.–max.: 26–73) volt. A felmérésben részt vettek 52%-a (n = 260) rendelkezett felsőfokú végzettséggel, és nagyobb részük (59%; n = 294) házasságban élt. A vizsgált populáció adatait a *2. táblázat* foglalja össze.

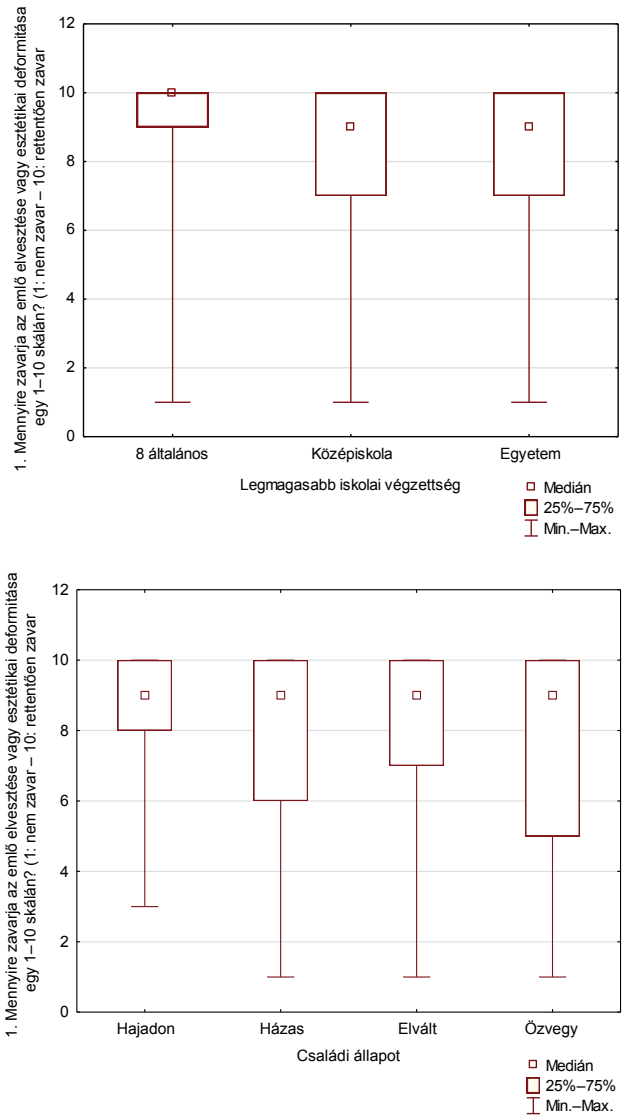
Érthetően az emlő elvesztése jelentősen zavarta a megkérdezetteket, az 1-től 10-ig terjedő skálán átlag 8 ± 3 (átlag ± standard deviáció [SD]) értéket adtak az erre a kérdésre vonatkozó válaszok; illetve a válaszok között sem az iskolai végzettség, sem a családi állapot tekintetében nem volt különbség *(1. ábra)*.

Az esetek közel kétharmadában (61%; n = 307) történt azonnali rekonstrukció, míg 167 beteg (33%) esetén az emlő-helyreállítás halasztott-azonnali módon történt, és a válaszadás a daganat eltávolítását követően hónapokkal vagy évekkel később, a rekonstrukció befejező lépésekor történt meg.

A válaszok alapján a megkérdezett nők 39%-a (n = 194) megelégedne a melltartóban szép dekoltázst eredményező emlőkkel, azonban 28%-uk (n = 140) az eredetinél szebb, 20%-uk (n = 99) pedig egyenesen tökéletes emlőket szeretne a rekonstrukciós folyamat végén. Az elvárások tekintetében szignifikáns összefüggés mutatkozott az iskolai végzettséggel: a magasabb iskolai végzettség magasabb elvárásokkal társult (p<0,05). A szimmetria tekintetében határozott véleményt képviseltek a

2. táblázat | A vizsgálatban részt vett betegek általános tulajdonságai

Életkor				
n	Átlag	Medián	Minimum	Maximum
485	48	47	26	73
Hiányzó adat = 15 (3%)				
A legmagasabb iskolai végzettség				
8 általános		Középiskola		Egyetem
7 (1%)		218 (44%)		260 (52%)
Hiányzó adat = 15 (3%)				
Családi állapot				
Hajadon		Házas	Elvált	Özvegy
52 (10%)		294 (59%)	119 (24%)	20 (4%)
Hiányzó adat = 15 (3%)				



1. ábra | Az emlő elvesztésének értékelése iskolai végzettség és családi állapot szerint (boxplot)

betegek, nem volt különbség sem a családi állapot, sem az iskolázottság tekintetében: a nők 70%-a (n = 348) kívánna a rekonstrukciós folyamat végén mezítelenül is nagyjából egyforma emlőket.

Az emlők optimális esztétikai végeredményéhez a felmérésben részt vevők 43%-a (n = 217) maximum kettő, 37%-a (n = 184) akár három vagy négy műtétet is vállalna.

A beavatkozások finanszírozásának kérdésében megoszlottak a vélemények: 44% (n = 220) szerint maximum három-négy, 21% (n = 107) szerint legfeljebb csak két műtétet kellene térítenie az egészségbiztosítónak, míg a betegek közel harmada (31%; n = 157) van azon az állásponton, hogy akármennyi beavatkozásra van is szükség, mindegyiket fizetnie kellene az állami biztosítónak. A középiskolai végzettségűek kevésbé tartják jogosnak állami finanszírozásból a több műtétet, az egyetemi végzettségűek inkább (p<0,05).

A betegek 55%-a (n = 275) gondolja úgy, hogy a helyreállított emlőknek az életkor miatt bekövetkező változása egyéni esztétikai, plasztikai sebészeti kérdést jelent, azonban 28% (n = 139) szerint ez akár évtizedek múlva is a rekonstrukciós műtétsorozat, tehát az onkológiai helyreállító sebészet és nem az esztétikai sebészet megoldandó feladatát képezi.

Egyértelmű állaspontot képviselnek a betegek a beavatkozást végző orvossal kapcsolatban: 90%-uk (n = 448) plasztikai sebészre bízná a rekonstrukciót, továbbá 86%-uk (n = 430) szerint a daganatos emlők korszerű ellátását speciálisan felkészült emlősebészeknek kellene végezniük a jelenlegi általános sebészeti ellátással szemben.

A válaszadók döntő többsége (79%; n = 394) nem tartja elfogadhatónak, hogy jelenleg Magyarországon csak egy-két, speciálisan felkészült emlősebészeti központ működik, míg 10% (n = 51) beletörődik a jelenlegi helyzetbe, és további 9% (n = 46) úgy vélekedik, hogy a jobb ellátás érdekében a magánellátás felé szükséges fordulni.

A betegek 96%-a (n = 481) szerint a gyógyulást érdemben befolyásolja, hogy emlősebész végzi-e a műtétet, 63% (n = 316) pedig egyenesen úgy gondolja, hogy ez az egyik legfontosabb tényező egészsége visszanyerése érdekében.

Megbeszélés

A modern onkoplasztikus szemlélet elterjedése paradigmaváltást eredményezett az emlőrák ellátásában [28–30]. A sebészi kezelés az emlődaganat eltávolítását jelentő műtéttől az emlők teljes helyreállítását is magában foglaló komplex, akár kétoldali műtétek vagy műtéti sorozatok felé mozdult el. Ez számos rendszerszintű feladatot vet fel, például azt, hogy az onkológiai kontrollokkal párhuzamosan folytatandó a rekonstruált emlők élethosszig tartó plasztikai sebészeti utánkövetése és szükséges kozmetikai korrekciói. A fenti igények, indikációk az emlő onkológiai ellátásában újszerűek, melyek pontos meghatározása, az ellátás feladatkörének és tárgyi, valamint humánerőforrás-kívánalmainak tisztázása a korszerű, betegközpontú ellátórendszer kialakítása és magas szintű, hosszú távú üzemeltetése céljából elengedhetetlen. Mindezek alapját képezi a betegek igényeinek és elvárásainak megismerése és elemzése.

A jelen tanulmány az emlő elvesztésén és rekonstrukciós folyamaton átesett nőbetegeknek a rendszerrel kapcsolatos igényeit és elvárásait mérte fel. Az eredményekből látható, hogy az emlő elvesztése iskolai végzettségtől és családi állapottól függetlenül jelentősen zavarja a nőbetegeket *(1. ábra)*. Ezek az adatok megfelelnek azoknak az eredményeknek, amelyeket munkacsoportunk 2014-ben közölt, 500 nőbeteg 2010 és 2011 közötti kérdőíves vizsgálata alapján [28]. A felmérés szerint a betegek 30%-a (n = 148) közepesen, 40%-a (n = 198) nagyon félt az emlő elvesztésétől, közel 50%-uk (46%; n = 224) szeretett volna rekonstrukciót, de erről szinte semmit (32%; n = 158) vagy nagyon keveset (56%; n = 279) tudtak [28]. Az intézetben folyó onkoplasztikus emlősebészeti tevékenység alapján, a 2017–2018-ban elvégzett ugyanazon kérdőíves felmérés megismétlése szerint a nők továbbra is ugyanúgy félnek az emlő elvesztésétől, de a korábbi adatokkal (10%; n = 48) szemben a megkérdezetteknek már a 30%-a (n = 152) ismerte az emlőrekonstrukciós lehetőségeket, mely információkat főleg a sebésztől (52%; n = 258) vagy az internetről (27%; n = 135) gyűjtötték be. Ezek alapján kimondható, hogy az emlő elvesztése jelentős mértékben terheli pszichésen az emlőrákos betegeket szociális helyzettől és iskolai végzettségtől függetlenül, tehát az onkoplasztikus ellátórendszer kiterjesztése hazánkban indokolt és szükséges. Az elmúlt 6–8 évben az onkoplasztikus szemlélet a magyar nők között elterjedt és ismertté vált, amivel párhuzamosan nő a lakosság igénye is erre a speciális egészségügyi szolgáltatásra, melyet az ellátórendszernek ki kell tudnia elégítenie.

A páciensek a műtétek esztétikai eredményét tekintve magas elvárással rendelkeznek, összesen a nők közel fele (48%; n = 239) szeretne az eredetinél is szebb (28%; n = 140) vagy tökéletes (20%; n = 99) emlőket a rekonstrukciós folyamat végén. A reális elvárásokkal kapcsolatban történő preoperatív betegfelvilágosítás kiemelt fontosságú, ugyanis az onkoplasztikus beavatkozások nem esztétikai műtétek, és bár technikájukból eredően gyakran az esztétikai műtétekkel megegyező, magas szintű eredményekre képesek, teljesen alárendeltek az onkológiai beavatkozásoknak (például a reszekció helye, mértéke, radioterápia stb.), így eredményességüket a plasztikai sebészeti beavatkozáson túl számos egyéb tényező is befolyásolja [31].

A felmérésben részt vett nőbetegek döntő része (70%; n = 348) családi állapottól és végzettségtől függetlenül kívánna a rekonstrukciós folyamat végén mezítelenül is nagyjából egyforma emlőket. Tekintettel arra, hogy a legtöbbször implantátumalapú postmastectomiás rekonstrukciók során a két emlő szerkezete különbözik, idővel az emlők aszimmetriája fokozódni fog, mivel a felvarrt saját egészséges emlő máshogy fog viselkedni biológiai tulajdonságai miatt, mint a csak implantátumból és bőrből álló emlő. Ez alapján a szimmetria időbeli változása miatti másodlagos műtéti igények jelennek meg a betegek részéről.

A kívánt magas kozmetikai eredményt a nők leginkább kettő, de maximum három-négy műtét segítségével szeretnék elérni, melyeket véleményük szerint az egészségbiztosítónak kellene térítenie. Egyészt a jövőben kerülni szükséges az onkológiai finanszírozású esztétikai műtéteket, aminek kérdésfelvetése is nehezen megoldandó etikai és szakmai problémát jelent, másrészt a műtéti so-

rozatból álló kezelés óriási megterhelést jelent az ellátórendszer számára, mintha több száz vagy ezer esettel nőne az emlőrák miatt operáltak éves száma. Jelenleg a rendszer ezt elemeiben képes, de összességében kérdéses-e, hogy képes lenne biztosítani, így ebben az irányban a betegek, a szakma és a szakmapolitika együttes munkájára van szükség.

A betegek sebészi kezelésüket specializált centrumokban, speciálisan képzett emlősebészekre bíznák, mert véleményük szerint gyógyulásukat ez érdemben befolyásolja. Az emlőrák kezelésében az emlősebész is önálló prognosztikai faktor [32], de a BU-ok hazai elterjesztése, minőségbiztosítása, valamint a BRESO-akkreditációval a betegek túlélése és életminősége is tovább javítható a XXI. században [7].

A hazánkban tapasztalt mastectomiát követő onkoplasztikus emlő-helyreállítás iránti igény megfelel a nemzetközi trendeknek: brit tanulmány szerint az emlőeltávolításra váró nőbetegek 50%-a [33], míg az *Ananian és mtsai* által végzett francia tanulmány szerint a megkérdezettek 81%-a szeretne rekonstrukciót [34]. A nemzetközi helyzethez hasonlóan vizsgálatunk alapján a magyar betegek fő információs forrása szintén a sebész, illetve az internet [35, 36]. Az érintett nők igényeinek megismerése, a megfelelő tájékoztatás, a hozzáférhetőség növelése, a betegutak megszervezése és az egészségügyi rendszer megfelelő strukturálása nélkülözhetetlen az onkoplasztikus emlőrákellátás magas szintű kiterjesztéséhez [37, 38].

Következtetések

A korszerű onkoplasztikus ellátás új, összetett, rendszerszintű onkológiai és helyreállító sebészeti szakmai kérdéseket vet fel, amelyek a betegek informáltságával, a humánerőforrás szakképzésével, az ellátórendszer kapacitásaival és a finanszírozásával kapcsolatos új feladatokat eredményeznek. Az emlőrákban szenvedő betegek jól képzett emlősebészek által szakmai központokban végzett korszerű műtéteket szeretnének, amelyektől testi és lelki gyógyulásukat bizalommal remélhetik.

Anyagi támogatás: A közlemény megírása, illetve a kutatómunka anyagi támogatásban nem részesült. A klinikai feldolgozás a 2019-es Témakiválósági Program (TUDFO/51757/2019-ITM) támogatásában részesült.

Szerzői munkamegosztás: A szerzők egyenlő mértékben vettek részt a kutatómunkában és a kézirat elkészítésében. A cikk végleges változatát valamennyi szerző elolvasta és jóváhagyta.

Érdekeltségek: A szerzőknek nincsenek érdekeltségeik.

Irodalom

[1] Kásler M, Ottó Sz, Kenessey I. The current situation of cancer morbidity and mortality in the light of the National Cancer Registry, Hungary. [A rákmorbiditás és -mortalitás jelenlegi helyzete a Nemzeti Rákregiszter tükrében.] Orv Hetil. 2017; 158: 84–89. [Hungarian]
[2] Sant M, Aareleid T, Berrino F, et al. EUROCARE-3: survival of cancer patients diagnosed 1990–94 – results and commentary. Ann Oncol. 2003; 14(Suppl 5): v61–v118.
[3] Berrino F, De Angelis R, Sant M, et al. Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995–1999: results of the EUROCARE-4 study. Lancet Oncol. 2007; 8: 773–783. [Correction: Lancet Oncol. 2007; 8: 868.]
[4] Cataliotti L, Costa A, Daly PA, et al. Florence statement on breast cancer, 1998: forging the way ahead for more research on and better care in breast cancer. Eur J Cancer 1999; 35: 14–15.
[5] EUSOMA. The requirements of a specialist breast unit. Position paper. Eur J Cancer 2000; 36: 2288–2293. [Correction: Eur J Cancer 2003; 39: 847.]
[6] Piccart M, Cataliotti L, Buchanan M, et al. Brussels Statement document. Eur J Cancer 2001; 37: 1335–1337.
[7] Kovács T, Rubio I, Markopoulos C, et al. Theoretical and practical knowledge curriculum for European Breast Surgeons. Eur J Surg Oncol. 2020; 46: 717–736.
[8] Wilson AR, Marotti L, Bianchi S, et al. The requirements of a specialist Breast Centre. Eur J Cancer 2013; 49: 3579–3587.
[9] Perry N, Broeders M, de Wolf C, et al. European guidelines for quality assurance in breast cancer screening and diagnosis. Fourth edition – summary document. Ann Oncol. 2008; 19: 614–622.
[10] Biganzoli L, Marotti L, Hart CD, et al. Quality indicators in breast cancer care: an update from the EUSOMA working group. Eur J Cancer 2017; 86: 59–81.
[11] Újhelyi M, Pukancsik D, Kelemen P, et al. Breast cancer care quality analysis of the National Institute of Oncology in Hungary according to the requirements of European Society of Breast Cancer Specialists (EUSOMA). [A European Society of Breast Cancer Specialists (EUSOMA) előírásainak megfelelő emlőrákellátás minőségbiztosítási elemzése az Országos Onkológiai Intézetben.] Orv Hetil. 2016; 157: 1674–1682. [Hungarian]
[12] Andree C, Farhadi J, Goossens D, et al. A position statement on optimizing the role of oncoplastic breast surgery. Eplasty 2012; 12: e40.
[13] Emiroğlu M, Sert I, İnal A. The role of oncoplastic breast surgery in breast cancer treatment. J Breast Health 2015; 11: 1–9.
[14] Macmillan RD, McCulley SJ. Oncoplastic breast surgery: what, when and for whom? Curr Breast Cancer Rep. 2016; 8: 112–117.
[15] Harnett A, Smallwood J, Titshall V, et al. Diagnosis and treatment of early breast cancer, including locally advanced disease – summary of NICE guidance. Br Med J. 2009; 338: b438.
[16] Makari-Judson G, Braun B, Jerry DJ, et al. Weight gain following breast cancer diagnosis: implication and proposed mechanisms. World J Clin Oncol. 2014; 5: 272–282.
[17] Nyrop KA, Williams GR, Muss HB, et al. Weight gain during adjuvant endocrine treatment for early-stage breast cancer: what is the evidence? Breast Cancer Res Treat. 2016; 158: 203–217.
[18] Raghavendra A, Sinha AK, Valle-Goffin J, et al. Determinants of weight gain during adjuvant endocrine therapy and association of such weight gain with recurrence in long-term breast cancer survivors. Clin Breast Cancer 2018; 18: e7–e13.
[19] Wolfe JN. Breast parenchymal patterns and their changes with age. Radiology 1976; 121(Part 1): 545–552.

[20] Nie K, Su MY, Chau MK, et al. Age- and race-dependence of the fibroglandular breast density analyzed on 3D MRI. Med Phys. 2010; 37: 2770–2776.
[21] Machida Y, Nakadate M. Breast shape change associated with aging: a study using prone breast magnetic resonance imaging. Plast Reconstr Surg Glob Open 2015; 3: e413.
[22] Momoh AO, Ahmed R, Kelley BP, et al. A systematic review of complications of implant-based breast reconstruction with prereconstruction and postreconstruction radiotherapy. Ann Surg Oncol. 2014; 21: 118–124.
[23] Nyerges G. Ethical implications of scientific human experiments. [Embereken végzett tudományos kutatások etikája.] Orv Hetil. 1985; 126: 1451–1458. [Hungarian]
[24] Gradishar WJ, Anderson BO, Balassanian R, et al. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2016; 14: 324–354.
[25] Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2015; 26(Suppl 5): 8–30.
[26] Lázár G, Bursics A, Farsang Z, et al. Modern surgical treatment of breast cancer. 3rd Hungarian Breast Cancer Consensus Conference – Surgery Guidelines. [III. Emlőrák Konszenzus Konferencia – Az emlőrák korszerű sebészi kezelése.] Magy Onkol. 2016; 60: 194–207. [Hungarian]
[27] Hammer Ø, Harper DA, Ryan PD. PAST: Paleontological Statistics software package for education and data analysis. Palaeontol Electron. 2001; 4: 1–9.
[28] Mátrai Z, Kenessey I, Sávolt A, et al. Evaluation of patient knowledge, desire, and psychosocial background regarding postmastectomy breast reconstruction in Hungary: a questionnaire study of 500 cases. Med Sci Monit. 2014; 20: 2633–2642.
[29] Pukancsik D, Kelemen P, Sávolt Á, et al. Evaluation of clinicopathological findings and cosmetic outcome of 100 immediate postmastectomy breast reconstruction cases. [Azonnali, postmastectomiás emlőrekonstrukciókkal szerzett tapasztalatok. Száz eset klinikopatológiai utánkövetése és a kozmetikai eredmények felmérése.] Orv Hetil. 2016; 157: 1830–1838. [Hungarian]
[30] Mátrai Z, Gulyás G, Tóth L, et al. Challenges in oncologic plastic surgery of the breast. [A modern emlősebészet onkoplasztikai kihívásai.] Magy Onkol. 2011; 55: 40–52. [Hungarian]
[31] Pukancsik D, Kelemen P, Újhelyi M, et al. Objective decision making between conventional and oncoplastic breast-conserving surgery or mastectomy: an aesthetic and functional prospective cohort study. Eur J Surg Oncol. 2017; 43: 303–310.
[32] Cataliotti L, De Wolf C, Holland R, et al. Guidelines on the standards for the training of specialised health professionals dealing with breast cancer. Eur J Cancer 2007; 43: 660–675.
[33] Keith DJ, Walker MB, Walker LG, et al. Women who wish breast reconstruction: characteristics, fears and hopes. Plast Reconstr Surg. 2003; 111: 1051–1056.
[34] Ananian P, Houvenaeghel G, Protière C, et al. Determinants of patients' choice of reconstruction with mastectomy for primary breast cancer. Ann Surg Oncol. 2004; 11: 762–771.
[35] Morrow M, Mujahid M, Lantz PM, et al. Correlates of breast reconstruction: results from a population-based study. Cancer 2005; 104: 2340–2346.
[36] Alderman AK, Hawley ST, Waljee J, et al. Understanding the impact of breast reconstruction on the surgical decision-making process for breast cancer. Cancer 2008; 112: 489–494.
[37] Flitcroft K, Brennan M, Spillane A. Making decisions about breast reconstruction: a systematic review of patient-reported factors influencing choice. Qual Life Res. 2017; 26: 2287–2319.
[38] Retrouvey H, Zhong T, Gagliardi AR, et al. How patient acceptability affects access to breast reconstruction: a qualitative study. BMJ Open 2019; 9: e029048.

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